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FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEETING OF THE PSYCHOPHARMACOLOGIC DRUGS
ADVISORY COMMITTEE (PDAC)

Tuesday, March 29, 2016
8:00 a.m. to 3:49 p.m.

FDA White Oak Campus
Building 31, The Great Room
White Oak Conference Center
Silver Spring, Maryland

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Meeting Roster

DESIGNATED FEDERAL OFFICER (Non-Voting)

Kalyani Bhatt, BS, MS

Division of Advisory Committee and
Consultant Management
Office of Executive Programs, CDER, FDA

PSYCHOPHARMACOLOGIC DRUGS ADVISORY COMMITTEE

MEMBERS (Voting)

David A. Brent, MD

(Chairperson)
Academic Chief
Division of Child Adolescent Psychiatry
University of Pittsburgh School of Medicine
Western Psychiatric Institute and Clinic
Pittsburgh, Pennsylvania

Thomas A. Grieger, MD

Staff Psychiatrist
Maryland Department of Health and Mental Hygiene
Thomas B. Finance Center
Cumberland, Maryland

1 **Dawn F. Ionescu, MD**

2 Depression Clinical and Research Program

3 Massachusetts General Hospital

4 Harvard Medical School

5 Boston, Massachusetts

6

7 **Rajesh Narendran, MD**

8 Associate Professor in Radiology and Psychiatry

9 University of Pittsburgh School of Medicine

10 Pittsburgh, Pennsylvania

11

12 **David Pickar, MD**

13 Adjunct Professor of Psychiatry

14 Johns Hopkins Medical School

15 Uniformed Services University of Health Sciences

16 Gabriel Sciences, LLC

17 Chevy Chase, Maryland

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Kim O. Witczak

(Consumer Representative)
Co-Founder, Executive Director
Woodymatters
Minneapolis, Minnesota

TEMPORARY MEMBERS (Voting)

John E. Duda, MD

Director, Parkinson's Disease Research
Education & Clinical Center
Philadelphia Veteran's Affairs Medical Center
Associate Professor of Neurology
Perelman School of Medicine
University of Pennsylvania
Philadelphia, Pennsylvania

1 **Susan Elmore, DVM, MS, DAVCP, DABT**

2 Pathologist and Staff Scientist

3 National Toxicology Program Pathology Group

4 Cellular and Molecular Pathology Branch

5 National Institute of Environmental Health Sciences

6 National Institutes of Health

7 Research Triangle Park, North Carolina

8
9 **Stanley Fahn, MD**

10 H. Houston Merritt Professor of

11 Neurology/Columbia University

12 Director Emeritus, Movement Disorder Division

13 Neurological Institute

14 New York, New York

15
16 **Tobias Gerhard, PhD, RPh**

17 Associate Professor

18 Rutgers University

19 Department of Pharmacy Practice and Administration

20 Ernest Mario School of Pharmacy

21 New Brunswick, New Jersey

22

1 **Linda Morgan, MBA, RPh**

2 *(Patient Representative)*

3 Asheville, North Carolina

4

5 **Urmimala Sarkar, MD**

6 Associate Professor in Residence

7 School of Medicine

8 University of California, San Francisco

9 San Francisco, California

10

11 **Christopher H. Schmid, PhD**

12 Professor of Biostatistics

13 Center for Evidence Based Medicine

14 Department of Biostatistics

15 Brown University School of Public Health

16 Providence, Rhode Island

17

18

19

20

21

22

1 **Almut Winterstein, RPh, PhD, FISPE**

2 Professor and Interim Chair

3 Pharmaceutical Outcomes & Policy

4 College of Pharmacy

5 Epidemiology, College of Public Health and

6 Health Professions and College of Medicine

7 University of Florida

8 Gainesville, Florida

9

10 **ACTING INDUSTRY REPRESENTATIVE TO THE COMMITTEE**

11 **(Non-Voting)**

12 **Mark Forrest Gordon, MD**

13 Director, Clinical Development and Medical Affairs

14 General Medicine / Central Nervous Systems &

15 Established Products

16 Boehringer Ingelheim Pharmaceuticals, Inc.

17 Ridgefield, Connecticut

18

19

20

21

22

1 **FDA PARTICIPANTS (Non-Voting)**

2 **Robert Temple, MD**

3 Deputy Director for Clinical Science

4 CDER, FDA

5 Deputy Director (Acting)

6 Office of Drug Evaluation-I (ODE-I)

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

8

9 **Mitchell Mathis, MD**

10 Director

11 Division of Psychiatry Products (DPP)

12 ODE-I, OND, CDER, FDA

13

14 **Tiffany R. Farchione, MD**

15 Deputy Director

16 DPP, ODE-I, OND, CDER, FDA

17

18 **Marc Stone, MD**

19 Deputy Director of Safety

20 DPP, ODE-I, OND, CDER, FDA

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Paul Andreason, MD

Medical Officer

DPP, ODE-I, OND, CDER, FDA

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P R O C E E D I N G S

(8:00 a.m.)

Call to Order

Introduction of Committee

1 DR. BRENT: Good morning. I'd like to first
2 remind everyone to please silence their cell phones
3 and any other devices, if you've not already done
4 so. And I would also like to identify the FDA
5 press contact, Chris Baumgartner.

6 My name is David Brent. I'm the chairperson
7 of the Psychopharmacological Drug Advisory
8 Committee, and I'll be chairing this meeting. I
9 will now call the Psychopharmacological Drug
10 Advisory Committee meeting to order. We'll start
11 by going around the table and introducing
12 ourselves. We'll start with the FDA to my left and
13 go around the table.

14 DR. TEMPLE: Good morning, everybody. I'm
15 Bob Temple, deputy director of ODE I.

16 DR. MATHIS: I'm Mitchell Mathis, director
17 of psychiatry products.

18 CAPT ANDREASON: I'm Paul Andreason. I am

1 the clinical reviewer for this NDA.

2 DR. DUDA: I'm John Duda. I'm a movement
3 disorder neurologist from the Philadelphia VA
4 Medical Center and the University of Pennsylvania.

5 DR. FAHN: I'm Stan Fahn, also a movement
6 disorder neurologist, Columbia University, New
7 York.

8 DR. NARENDRAN: Raj Narendran, psychiatrist,
9 University of Pittsburgh.

10 DR. IONESCU: Dawn Ionescu, psychiatrist at
11 Massachusetts General Hospital.

12 MS. BHATT: Good morning. I'm Kalyani
13 Bhatt. I'm the designated federal officer with the
14 Division of Advisory Committee and Consultant
15 Management.

16 DR. PICKAR: Dave Pickar, psychiatrist,
17 former chief experimental therapeutics, intramural
18 NIMH, adjunct professor, Hopkins.

19 MS. WITCZAK: Good morning. Kim Witczak,
20 consumer representative.

21 DR. GRIEGER: Tom Grieger, clinical
22 psychiatrist for the state of Maryland and

1 professor of psychiatry at Uniformed Services
2 University.

3 DR. SCHMID: Chris Schmid, professor of
4 biostatistics, Brown University.

5 MS. MORGAN: Linda Morgan, patient.

6 DR. WINTERSTEIN: Almut Winterstein. I'm
7 chair of DSaRM, and I'm professor and chair for
8 pharmaceutical outcomes and policy at the
9 University of Florida.

10 DR. GERHARD: Tobias Gerhard,
11 pharmacoepidemiologist at Rutgers University.

12 DR. ELMORE: Susan Elmore, veterinarian
13 toxicologic pathologist for the National Toxicology
14 Program.

15 DR. GORDON: Mark Gordon, industry
16 representative, Boehringer Ingelheim
17 Pharmaceuticals.

18 DR. BRENT: I am reintroducing myself
19 because it wasn't recorded. My name is David
20 Brent. I'm a psychiatrist at the University of
21 Pittsburgh School of Medicine. And now, I'm going
22 to read the following.

1 For topics such as those being discussed at
2 today's meeting, there are often a variety of
3 opinions, some of which are quite strongly held.
4 Our goal is that today's meeting will be a fair and
5 open forum for discussion of these issues and those
6 individuals can express their views without
7 interruption. Thus, as a gentle reminder,
8 individuals will be allowed to speak into the
9 record only if recognized by the chairperson. We
10 look forward to a productive meeting.

11 In the spirit of the Federal Advisory
12 Committee Act and the Government in the Sunshine
13 Act, we ask that the advisory committee members
14 take care that their conversations about the topic
15 at hand take place in the open forum of the
16 meeting.

17 We are aware that the members of the media
18 are anxious to speak with the FDA about these
19 proceedings. However, the FDA will refrain from
20 discussing the details of this meeting with the
21 media until its conclusion. Also, the committee is
22 reminded to please refrain from discussing the

1 meeting topic during breaks or lunch. Thank you.

2 Now, I'll pass to Kalyani Bhatt who will
3 read the conflict of interest statement.

4 **Conflict of Interest Statement**

5 MS. BHATT: The Food and Drug Administration
6 is convening today's meeting of the
7 Psychopharmacologic Drugs Advisory Committee under
8 the authority of the Federal Advisory Committee
9 Act, FACA, of 1972. With the exception of the
10 industry representative, all members and temporary
11 voting members of the committee are special
12 government employees, SGEs, or regular federal
13 employees from other agencies and are subject to
14 federal conflict of interest laws and regulations.

15 The following information on the status of
16 this committee's compliance with federal ethics and
17 conflicts of interest laws, covered by but not
18 limited to those found in 18 U.S.C. Section 208, is
19 being provided to participants in today's meeting
20 and to the public. FDA has determined that members
21 and temporary voting members of this committee are
22 in compliance with federal ethics and conflict of

1 interest laws.

2 Under 18 U.S.C. Section 208, Congress has
3 authorized FDA to grant waivers to special
4 government employees and regular federal employees
5 who have potential financial conflicts when it's
6 determined that the agency's need for a particular
7 individual's services outweighs his or her
8 potential financial conflict of interest.

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

20 Today's agenda involves a discussion of the
21 specific risk/benefit profile for new drug
22 application, NDA, 207318, Nuplazid, pimavanserin,

1 17-milligram immediate-release film-coated oral
2 tablets submitted by Acadia Pharmaceuticals, for
3 the proposed treatment of psychosis associated with
4 Parkinson's disease. This is a particular matters
5 meeting during which specific matters relating to
6 Nuplazid will be discussed.

7 Based on the agenda for today's meeting and
8 all financial interests reported by the committee
9 members and temporary voting members, no conflict
10 of interest waivers have been issued in connection
11 with this meeting.

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

16 With respect to the FDA's invited industry
17 representative, we'd like to disclose that Dr. Mark
18 Forrest Gordon is participating in this meeting as
19 a nonvoting industry representative acting on
20 behalf of regulated industry. Dr. Gordon's role at
21 this meeting is to represent industry in general
22 and not any particular company. Dr. Gordon is

1 employed by Boehringer Ingelheim.

2 We'd like to remind members and temporary
3 voting members that if the discussions involve any
4 other products or firms not already on the agenda
5 for which an FDA participant has a personal or
6 imputed financial interest, the participants need
7 to exclude themselves from such involvement, and
8 their exclusion will be noted for the record.

9 FDA encourages all other participants to
10 advise the committee of any financial relationships
11 that they may have with the firm at issue. Thank
12 you.

13 DR. BRENT: We will now proceed with the
14 first introductory remarks presented by Dr. Mathis,
15 who is the division director, followed by the
16 applicant presentations.

17 **FDA Opening Remarks**

18 DR. MATHIS: Good morning. My name is Mitch
19 Mathis. I'm the director of psychiatry products
20 here at FDA, and I'd like to welcome the committee.
21 We appreciate you being here. We're going to need
22 to have some good discussion with you about this

1 drug application. And the public audience, welcome
2 to you as well. Today we're going to discuss
3 pimavanserin for the treatment of Parkinson's
4 disease psychosis.

5 Now, about the drug, pimavanserin is, in
6 terms of its pharmacology, a 5-HT_{2A} inverse
7 agonist, which is different than the usual atypical
8 antipsychotics. But because we as psychiatrists
9 tend to name new groups of drugs as being not the
10 old group of drugs, we had typical antipsychotics
11 and then atypical antipsychotics, this drug at
12 least for now is an atypical antipsychotic, but its
13 pharmacology is different than the other drugs.

14 As a 5-HT_{2A} inverse agonist without
15 dopaminergic activity, it's a drug that was used by
16 the sponsor to put into patients who need their
17 dopamine activity for the other parts of their
18 disease to be treated. So it makes some
19 pharmacologic logical sense to have a drug with a
20 different mechanism of action for this disease.

21 In terms of the disease, Parkinson's disease
22 psychosis affects up to 40 percent of patients who

1 have Parkinson's disease. And the reason that it's
2 important -- there are many reasons, primarily
3 because it's distressing for the patient and their
4 caregivers, but it's also distressing to public
5 health officers because the psychosis is often a
6 harbinger of nursing home placement. And nursing
7 home placement is often a harbinger of death for
8 this patient population, so treatment is an
9 important thing.

10 In terms of the NDA review, we granted
11 breakthrough therapy designation for this drug
12 early on because we have no other FDA-approved
13 drugs to treat this, and we've given it a priority
14 review, which means that we're at the advisory
15 committee early to discuss this.

16 You'll see from the presentations that they
17 have the majority of their efficacy data from a
18 single study, but there were, of course, other
19 studies in the development program, and we'll show
20 those to you.

21 So for today, the sponsor will present their
22 drug, and then my team will present our take on the

1 efficacy and safety of their drug. And then, my
2 deputy director of safety will discuss the overall
3 work that was done with atypical antipsychotics
4 that resulted in the box warning for increased
5 morbidity and mortality in the elderly. We think
6 that that's relevant here.

7 Then in the end, we'll ask the voting
8 members on the PDAC to vote on three questions, and
9 they are our usual three questions. The first one
10 is, has the applicant provided substantial evidence
11 of the effectiveness of pimavanserin for the
12 treatment of psychosis associated with Parkinson's
13 disease?

14 The second question is, has the applicant
15 adequately characterized the safety profile for
16 pimavanserin? And then, the third question will
17 be, do the benefits of pimavanserin for the
18 treatment of psychosis associated with Parkinson's
19 disease outweigh the risk of treatment?

20 So with that, I'll get out of the way and
21 turn the meeting back over to the chair. Thank
22 you.

1 DR. BRENT: Both the FDA and the public
2 believe in a transparent process for the
3 information-gathering and decision-making. To
4 ensure such transparency at the advisory committee
5 meeting, the FDA believes that it is important to
6 understand the context of an individual's
7 presentation.

8 For this reason, the FDA encourages all
9 participants, including the sponsor's nonemployee
10 presenters, to advise the committee of any
11 financial relationships that they may have with the
12 firm at issue, such as consulting fees, travel
13 expenses, honoraria, and interest in the sponsor,
14 including equity interest and those based upon the
15 outcome of the meeting.

16 Likewise, the FDA encourages you at the
17 beginning of your presentation to advise the
18 committee if you do not have any such financial
19 relationships. If you choose not to address this
20 issue of financial relationships at the beginning
21 of your presentation, it will not preclude you from
22 speaking.

1 We will now proceed with the applicant's
2 presentations.

3 **Applicant Presentation - Michael Monahan**

4 MR. MONAHAN: Dr. Brent, members of the
5 advisory committee, and FDA staff, good morning.
6 Acadia Pharmaceuticals is a San Diego-based
7 biopharmaceutical company focused on the
8 development of medicines to address unmet needs for
9 CNS disorders. It is our pleasure to be here
10 today, and we thank the advisory committee members
11 and the FDA for providing the opportunity to
12 present our data in support of Nuplazid for the
13 treatment of Parkinson's disease psychosis.

14 My name is Michael Monahan, and I'm director
15 of regulatory affairs at Acadia. This morning, I
16 will highlight some pimavanserin program background
17 specifics and preview the topics for our
18 presentation.

19 Pimavanserin has been submitted for the
20 indication of the treatment of psychosis associated
21 with Parkinson's disease. The specific proposed
22 language is shown on this slide in italics.

1 The recommended dose of pimavanserin is
2 34 milligrams taken orally as two 17-milligram
3 tablets once daily. Pimavanserin offers a novel
4 approach to the treatment of psychosis. It is a
5 highly selective and potent serotonin inverse
6 agonist with pharmacological activity driven
7 through its blockade of 5-HT_{2A} receptors.

8 Pimavanserin has no measurable activity at
9 most other CNS receptors, including dopaminergic,
10 histaminergic, adrenergic, or muscarinic receptors,
11 limiting its potential off-target effects. In
12 particular, pimavanserin would be the first
13 antipsychotic to have no effect on dopamine
14 receptors, and thus there is no mechanistic
15 rationale for a negative impact on Parkinson's
16 disease motor symptoms.

17 Pimavanserin is the first compound to be
18 developed and submitted for the treatment of
19 Parkinson's disease psychosis. Throughout the
20 clinical program, we worked closely with the FDA
21 and are grateful for their collaboration, which led
22 to the following key agreements: in the early

1 development program, the SAPS H and D scale chosen
2 as the primary measure of psychosis and the UPDRS
3 Parts II and III scale as a key secondary safety
4 assessment; the final design of phase 3 study 020,
5 including the use of the shortened PD specific
6 SAPS-PD scale as the primary endpoint; and
7 submission of the pimavanserin NDA based on the
8 results of study 020 with supportive data from the
9 earlier studies. This agreement was reached
10 following the agency's review of study 020 data in
11 2013.

12 Subsequently, the pimavanserin program for
13 Parkinson's disease psychosis was granted
14 breakthrough therapy designation. This designation
15 recognizes the potential of a drug to treat a
16 serious condition in which it has shown preliminary
17 clinical evidence that the drug may provide
18 substantial benefit over existing therapies.

19 The NDA was submitted in September 2015, and
20 it was accepted with priority review last November.
21 The NDA included data from 25 clinical studies in
22 the pimavanserin program representing the largest

1 Parkinson's disease psychosis database to date.
2 This includes four placebo-controlled studies in
3 Parkinson's disease psychosis subjects, including
4 an initial 4-week proof of concept study,
5 study 006, and three 6-week controlled studies,
6 studies 012, 014, and pivotal study 020. Two open
7 label extension trials enrolled subjects that
8 completed placebo-controlled studies, and study 015
9 is ongoing today.

10 In total, over 1200 subjects have been
11 exposed to pimavanserin, and about half of those
12 were Parkinson's disease psychosis subjects. Close
13 to 500 rolled into the extension studies with 250
14 and 170 subjects completing one and two years of
15 treatment, respectively.

16 Parkinson's disease psychosis is a
17 progressive and debilitating condition with serious
18 consequences for both patients and caregivers, and
19 there are no FDA-approved treatment options.
20 Today, we will present data to demonstrate that
21 pimavanserin has antipsychotic efficacy, which is
22 clinically meaningful and has been observed

1 consistently across multiple endpoints as well as
2 perspectives, including those of central, blinded
3 rating professionals, site-based physicians,
4 caregivers, and patients.

5 Tolerability of pimavanserin has been
6 evaluated with an acceptable safety profile for
7 this patient population, and while imbalances in
8 SAEs and deaths have been observed, as you'll see,
9 we've been unable to identify any unifying
10 pathophysiologic processes.

11 The majority of reported events are aligned
12 with events and risk factors that would be expected
13 in a frail, elderly population with the background
14 disease characteristics seen in PD patients.

15 Pimavanserin offers an important advancement
16 in the treatment of Parkinson's disease psychosis
17 with an overall positive benefit/risk profile. The
18 agenda for our presentation is shown on this slide.

19 I'd like to now introduce Dr. Stuart
20 Isaacson. Dr. Isaacson is a neurologist and
21 movement disorder specialist who routinely sees
22 patients with Parkinson's disease psychosis. He

1 will provide background on this disease and the
2 issues that physicians routinely face with attempts
3 in treatment. Dr. Isaacson.

4 **Applicant Presentation - Stuart Isaacson**

5 DR. ISAACSON: Thank you.

6 Good morning. I'm Dr. Stuart Isaacson, and
7 I'm the director of the Parkinson's Disease and
8 Movement Disorders Center in Boca Raton, Florida.
9 We have a large clinic and also provide access to
10 clinical trials, looking for better treatments for
11 our patients with Parkinson's disease.

12 In disclosure, I was an investigator in the
13 pimavanserin development program, and I've received
14 compensation for this research and consulting
15 activities from Acadia Pharmaceuticals, but I have
16 no equity interest in this or other companies.

17 This morning, I will provide an overview of
18 Parkinson's disease psychosis, or PD psychosis, and
19 discuss its debilitating impact on our patients,
20 their caregivers, and their families, and the
21 challenges it poses for clinicians, as we do not
22 have an effective and safe treatment option for our

1 patients that allows us to continue to treat their
2 motor symptoms.

3 Almost 1 million people in the U.S. have
4 Parkinson's disease. As many of you know, we've
5 traditionally thought of Parkinson's disease as
6 predominantly degeneration of dopamine neurons in
7 the substantia nigra, resulting in motor symptoms
8 of slowness, stiffness, tremor, and imbalance.

9 But over the past decade or two, it's become
10 apparent that Parkinson's disease is much more than
11 motor symptoms. Indeed, a range of non-motor
12 symptoms occur, reflecting widespread
13 neuropathology and derangement of multiple
14 neurotransmitter systems. Non-motor symptoms can
15 include orthostatic hypotension, constipation,
16 daytime sleepiness, and neuropsychiatric symptoms
17 with anxiety, depression, dementia, and psychosis.
18 And over the decades-long course of Parkinson's
19 disease, both the motor and non-motor symptoms are
20 progressive, and together, they significantly
21 impact our patients' daily activities and overall
22 quality of life.

1 PD psychosis is a common non-motor symptom,
2 perhaps occurring at some point in 25 to 60 percent
3 of our patients, prevalence increasing with disease
4 duration and severity in this aging, elderly, and
5 frail population. It's been estimated that perhaps
6 half of patients with PD psychosis require
7 pharmacologic treatment. PD psychosis increases
8 the risk of morbidity and mortality and is a major
9 reason for hospitalization and for nursing home
10 placement.

11 While we've thought over the years that
12 dopaminergic medications can trigger these
13 symptoms, a number of studies have failed to find a
14 clear association between the dose or class of
15 medications. Like most non-motor symptoms, PD
16 psychosis is an inherent part of the underlying
17 synuclein neurodegenerative process, probably
18 involving serotonergic dysfunction with evidence of
19 involvement of 5-HT_{2A} receptors.

20 Our patients are already burdened with
21 increasing PD motor symptoms, and now they have to
22 contend with superimposed psychosis symptoms.

1 In 2005, a consensus meeting was held at
2 NIH. This meeting highlighted that PD psychosis is
3 a discrete syndrome, distinct from delirium and
4 from the psychoses of other disorders and also that
5 PD psychosis probably reflects the underlying
6 neurodegenerative process and that dopaminergic
7 medications were not sufficient and may not be
8 necessary for the development of psychosis in PD.

9 Diagnostic criteria for PD psychosis were
10 established and later published in Movement
11 Disorders. Criteria highlight the mainly positive
12 symptoms of psychosis and require a diagnosis of
13 Parkinson's disease for at least one year with the
14 onset of psychosis beginning after PD diagnosis and
15 lasting for greater than one month.

16 The consensus meeting also led the Movement
17 Disorder Society task force on rating scales in PD
18 to critically evaluate scales for PD psychosis.
19 Published in 2008, the task force recommended four
20 rating scales as being useful for clinical trials
21 and a need to develop a new scale more specific for
22 the distinct symptom complex of PD psychosis.

1 The hallmark symptoms of PD psychosis are
2 the positive symptoms of hallucinations and
3 delusions. Illusions and false sense of presence
4 are also common. In one study by Chou and
5 associates, one of the larger studies that looked
6 at approximately 160 patients with PD psychosis,
7 98 percent had hallucinations, most commonly
8 visual, and 76 percent developed illusions.

9 But it's not just the presence of these
10 symptoms that define PD psychosis in our patients.
11 For instance, when psychosis emerges, our patient
12 may see snakes on the bedroom floor once or twice a
13 week and may retain insight, knowing the snakes are
14 not real. But over time, PD psychosis invariably
15 progresses, and we have to evaluate its effects on
16 our patients.

17 For instance, has insight been lost? Does
18 our patient now believe the snakes are real and
19 runs to the door to escape them? Are symptoms more
20 frequent? Is there a patient who is seeing a dog
21 quietly lying on a bedroom floor once a week now
22 seeing that dog every day? Are symptoms more

1 severe or troublesome? Are there now multiple dogs
2 now growling or climbing onto the bed?

3 Do these symptoms impact the daily lives of
4 our patients and their caregivers? Does the
5 patient now not want to leave their bed for fear
6 the growling dogs will bite or places dishes of dog
7 food throughout the house causing a risk of falls?
8 Or is our patient becoming agitated or aggressive
9 with caregivers and family, trying to escape
10 menacing snakes or dogs, barricading doorways or
11 calling 911?

12 So when we actually begin to think about
13 treatment options and responses to treatment, we
14 have to consider the insight, frequency, severity,
15 and the impact psychosis has on each one of our
16 patients and their daily lives. And as you will
17 hear about later this morning, the SAPS items used
18 in the trials that we participated in also reflect
19 these types of issues that we see in the clinic.

20 Several individual items evaluate the
21 frequency of hallucinations and delusions, and
22 other items are global questions reflecting the

1 severity of delusions and of hallucinations seen
2 here on this slide.

3 For example, imagine a patient who sees
4 small children several times a week who crowd in
5 the living room, block the TV, and annoy her. This
6 may be scored as a 4 on the SAPS global
7 hallucinations item seen here. Improving even one
8 point on this question to a 3 could be significant.

9 If treatment could make the children be seen
10 just once or twice a week, who just stand to the
11 side and smile, this could be meaningful for our
12 patient and probably for her caregiver as well.

13 PD psychosis is a debilitating condition.
14 My patients already contend with difficulty with
15 moving and walking and balance and trouble using
16 their hands for everyday activities such as writing
17 and eating. And then PD psychosis emerges, and it
18 can begin to overshadow these advancing motor
19 symptoms.

20 The consequences of PD psychosis are
21 significant. A patient with PD psychosis is very
22 different than a patient without. That's partly

1 because one of our major approaches to a patient
2 with PD psychosis is to lower the dopamine
3 medicines that help their mobility. So not only do
4 our patients suffer with psychosis but now they
5 also have worsening mobility due to our lowering of
6 their Parkinson's medications for lack of a better
7 option.

8 Psychosis can also disrupt family and daily
9 life, affect relationships with caregivers. It's
10 emotionally distressing, sometimes frightening to
11 see or feel things that aren't real. Patients
12 often become isolated, withdrawing from social
13 activities and support groups, and important
14 exercise needed for PD mobility. And this all
15 leads to a significant impact on quality of life.

16 Among all the motor and non-motor symptoms
17 of Parkinson's disease, PD psychosis is a major
18 stressor on caregivers and affects their physical
19 and emotional health as well. It's also important
20 to consider that these are caregivers and families
21 who have spent the journey of Parkinson's disease,
22 often over a decade, of helping their loved ones

1 with progressive mobility problems and managing
2 polypharmacy.

3 So with the onset of psychosis, everything
4 now becomes even much more difficult. As seen in
5 this study, caregivers of patients with PD
6 psychosis had greater caregiver burden and greater
7 distress. And very frequently, delusions are
8 actually directed specifically at caregivers with a
9 feeling of spousal infidelity even after 50 years
10 of marriage, or that a longtime health aide is now
11 stealing money. These cause a great deal of stress
12 on the caregiver-patient relationship.

13 Remarkably, in one study, PD psychosis was
14 the reason for 24 percent of all hospitalizations
15 of PD patients and was a major cause of prolonged
16 hospitalization and of hospital readmission.
17 Perhaps most importantly, PD psychosis is a major
18 trigger for a PD patient to enter a long-term care
19 facility.

20 As seen in this study, there's an increased
21 risk of nursing home admission in PD patients with
22 psychosis compared to those without. Nursing home

1 placement can reflect a combination of psychosis
2 symptoms, caregiver burden, and also, worsening
3 mobility due to needing to reduce their dopamine
4 medications. And most often, long-term care
5 facility placement is permanent.

6 PD psychosis is also an independent risk
7 factor for mortality in our patients with PD. In
8 this long-term study of PD patients, those with
9 psychosis at baseline or who develop psychosis in
10 the study had significantly increased mortality.
11 At one year, mortality was 7 percent, and by three
12 years, mortality was 40 percent.

13 Our current clinical approach, though, to
14 treating our patients with PD psychosis is
15 suboptimal. We need to minimize polypharmacy,
16 including anticholinergics, sedatives, and
17 hypnotics. We try to identify and treat any
18 triggering, systemic illnesses like urinary or
19 other infections and dehydration, all of which are
20 common in this aging population, and we try non-
21 pharmacologic therapies.

22 Unfortunately, with the lack of effective

1 treatment options, we often have to reduce or
2 choose not to increase dopaminergic therapy, which
3 worsens motor function and can affect balance and
4 lead to falls. And it's not even clear that
5 reducing PD medication is effective. Most of our
6 patients will continue to have psychosis symptoms
7 that recur over time.

8 When PD psychosis persists or limits
9 dopaminergic therapy, we resort to the empiric use
10 of off-label antipsychotics as there is no
11 FDA-approved treatment for PD psychosis. The
12 off-label use for atypical antipsychotics for PD
13 psychosis, though, is problematic.

14 Most of the approved antipsychotics block
15 dopamine receptors and worsen motor Parkinson's.
16 There's a black box warning for increased mortality
17 in the elderly with dementia, and our patients with
18 PD psychosis are at increased risk of developing
19 dementia. One recent study from Weintraub, et al.
20 found increased mortality in PD patients with
21 psychosis treated with currently available typical
22 and atypical antipsychotics.

1 These antipsychotics have side effects that
2 reflect their receptor profile and can worsen
3 non-motor PD symptoms such as somnolence,
4 orthostatic hypotension, constipation, and
5 drooling, and have class associated risks of
6 neuroleptic sensitivity, neuroleptic malignant
7 syndrome, and metabolic syndrome. And so, their
8 use often comes at a price for our patients.

9 Yet despite these issues, almost half of
10 patients with PD psychosis are prescribed an
11 antipsychotic, and in these two studies from
12 Dr. Weintraub and associates, many were prescribed
13 antipsychotics known to worsen motor function.

14 You see, unlike schizophrenia where patients
15 have normal presynaptic dopamine production, the
16 severe dopamine depletion in Parkinson's disease
17 makes our patients readily and rapidly have
18 worsening motor function when exposed to any of the
19 typical or atypical antipsychotics that are
20 antagonists at post-synaptic dopamine D2 receptors.

21 For this reason, guidelines from the
22 Movement Disorder Society and the American Society

1 of Geriatrics Beers criteria caution against the
2 use of any antipsychotic, other than quetiapine,
3 used most frequently in these studies, or
4 clozapine, which is rarely used.

5 Only olanzapine, quetiapine, and clozapine
6 have been evaluated for PDP in controlled trials.
7 Olanzapine, like other D2 antagonists,
8 significantly worsens motor symptoms and also is
9 not effective. Quetiapine is most commonly used
10 clinically, yet failed to demonstrate efficacy in
11 four smaller trials and often has a dose-limiting
12 side effect of excessive sedation, can provoke
13 orthostatic hypotension, and in one study, almost
14 25 percent developed neuroleptic sensitivity
15 reactions. And no safety information is available
16 beyond 12 weeks in PD patients.

17 Clozapine demonstrated efficacy in an early
18 case series and in two 4-week controlled trials.
19 However, clozapine is rarely used. This is because
20 in addition to sometimes limiting side effects of
21 sedation, orthostatic hypotension, and drooling,
22 there is a 1 to 2 percent risk of agranulocytosis.

1 Prescribers and patients must enroll in a
2 national registry, and a blood count is checked
3 prior to each and every clozapine refill, weekly
4 for six months, biweekly for six months, then
5 monthly. This poses an enormous logistical burden
6 on patients with impaired mobility to get to both
7 the lab and pharmacy each week. It's also a
8 considerable challenge for clinical staff. For all
9 these reasons, clozapine is used in less than 2
10 percent in patients with PD psychosis.

11 So we're really in a therapeutic bind today
12 in trying to treat our patients with PD psychosis.
13 We want to take better care of our patients, and we
14 want to choose our treatments wisely and
15 thoughtfully. PD psychosis is debilitating,
16 burdensome, and significantly complicates the lives
17 of our patients already contending with advancing
18 motor symptoms.

19 PD psychosis is also a significant challenge
20 to our clinical management, leading to reduced PD
21 medicines and worsened mobility and to an increased
22 risk of hospitalization, nursing home placement,

1 and mortality. Current antipsychotics either
2 worsen motor symptoms, lack efficacy, or have
3 serious risks that require intensive blood
4 monitoring.

5 Our patients need an effective and safe
6 therapy for PD psychosis to improve even partially
7 the frequency and severity of hallucinations and
8 delusions and to do so without compromising their
9 motoric function.

10 I'd like now to introduce Dr. Serge
11 Stankovic.

12 **Applicant Presentation - Serge Stankovic**

13 DR. STANKOVIC: Good morning. My name is
14 Serge Stankovic. I'm executive vice president of
15 research and development at Acadia Pharmaceutical
16 and psychiatrist and epidemiologist by training. I
17 will present data supporting the efficacy of
18 pimavanserin in Parkinson's disease psychosis.

19 Pimavanserin is a highly selective inverse
20 agonist with high affinity for 5-HT2A receptor.
21 The 5-HT2C receptor is the only other receptor
22 targeted by pimavanserin but with more than tenfold

1 lower selectivity compared to 5-HT_{2A}. The
2 biological rationale for utility of 5-HT_{2A} inverse
3 agonist for treatment of psychotic symptoms is
4 based on observation that visual hallucinations are
5 associated with excessive 5-HT_{2A} transmission in
6 the areas responsible for visual processing and
7 that the number of 5-HT_{2A} receptors is increased in
8 the sensory cortex of patients experiencing
9 psychotic symptoms.

10 In contrast to other antipsychotics,
11 pimavanserin does not exhibit measurable binding to
12 dopaminergic, histaminergic, adrenergic, or
13 muscarinic receptors that are individually or
14 collectively associated with significant dose-
15 limiting side effects. Specifically, D₂ receptor-
16 related risks include extra-pyramidal symptoms and
17 cognitive dulling. H₁ receptor-mediated side
18 effects include sedation. Alpha 1 adrenergic-
19 related side effects include postural hypotension,
20 and muscarinic-related side effects include
21 sialorrhea. Based on the promising pharmacologic
22 profile of pimavanserin, we took it into clinical

1 development.

2 Study 006 was our initial visibility and
3 proof of principle study in Parkinson's disease
4 psychosis. This small 60-patient, flexible dose
5 study met its primary objective on motor symptoms
6 and provided a signal of antipsychotic efficacy
7 without indication of a negative impact on motor
8 function.

9 Following study 006, we initiated two
10 multiple dose phase 2b/3 clinical studies.
11 Study 012, which evaluated the higher end of the
12 dose range, was completed first but did not meet
13 its primary objective. Subsequently, the sister
14 study 014, which evaluated lower doses, was
15 terminated prematurely on the basis of study 012
16 results.

17 Nevertheless, these studies provided
18 valuable design lessons and encouraging signals of
19 efficacy that ultimately led to a decision to move
20 forward and initiate the phase 3 study, our pivotal
21 study 020.

22 In order to evaluate the long-term safety of

1 pimavanserin, we conducted two open label studies.
2 Study 010 was an extension of study 006, and
3 study 015 enrolled patients that completed placebo
4 studies 012, 014, or 020.

5 I will present informative data from the
6 completed phase 2b/3 study 012 followed by a
7 complete review of the efficacy results from the
8 pivotal study 020.

9 Study 012 was a 6-week, randomized,
10 double-blind, placebo-controlled study that
11 evaluated two doses of pimavanserin, 8.5 milligrams
12 and 34 milligrams. The study enrolled PD psychosis
13 patients with moderate psychotic symptoms. The
14 primary endpoint in this study was Scale for
15 Assessment of Positive Symptoms Hallucinations and
16 Delusions module, or SAPS H plus D, a validated,
17 20-item rating scale for assessment of symptom
18 severity in psychotic patients.

19 Study 012 was a global study conducted in
20 three regions. It is important to note that in
21 this study, two different methods were used for
22 assessment of primary outcome. Specifically,

1 real-time video interviews by centralized,
2 independent, blinded raters were used in the United
3 States. Due to a lack of technical capabilities in
4 Europe and India, local site raters performed SAPS
5 H plus D ratings. In retrospect, this was a
6 methodological inconsistency that confounded
7 already existing differences between the regions.

8 At the end of the study, pimavanserin failed
9 to separate from the placebo on the primary
10 endpoint. We did observe a meaningful average
11 change from baseline of around 6 points in the
12 pimavanserin group. However, a high placebo
13 response was observed in the two regions where SAPS
14 H plus D ratings were not centralized, resulting in
15 the lack of separation between treatment arms.

16 In the prospectively defined secondary
17 analysis by region, meaning the U.S., Europe, and
18 India separately, we saw, however, a different
19 picture.

20 Here are the results from the regional
21 analysis. In the U.S., shown on the left, the
22 average change from baseline in the pimavanserin

1 34-milligram group was around 7 points. The
2 difference from placebo was 2.5, showing a trend
3 for superiority with a p-value of 0.099.

4 In the other two regions, the pimavanserin
5 34-milligram dose performed as in the U.S., but the
6 placebo arm showed either similar or larger
7 response. The other doses tested, the
8 8.5 milligram, did not show a signal of efficacy in
9 any of the regions.

10 What contributed to the observed discrepancy
11 in response between the regions? Cultural and
12 medical practice differences certainly could have
13 an impact. It is also possible, however, that use
14 of a different methodology for the assessment of
15 the primary endpoint in the U.S. versus two other
16 regions could have affected the outcome.

17 So we looked more closely at the U.S.
18 region. We observed that pimavanserin 34-milligram
19 group showed a consistently larger response over
20 placebo, a nominal difference of 2 to 2 and a half
21 points starting at week two and continuing
22 throughout the duration of the study. This

1 difference did not reach statistical significance,
2 but the magnitude of the average difference
3 approach a clinical meaningful effect.

4 Our experience with studies 006, 012 and 014
5 provided key learnings that informed the design of
6 the pivotal trial, namely, the totality of data
7 suggested the 34-milligram dose would be
8 appropriate target dose. Brief psychosocial
9 therapy, or BPST, during screening phase should be
10 employed to manage symptoms in the absence of
11 pharmacologic therapy and to ensure that only
12 patients who still require antipsychotic treatment
13 are entered into the randomized portion of the
14 study.

15 Three, expectation and attention bias and
16 consequent placebo response may be reduced by
17 limiting the number of study arms, number of study
18 visits, and assessments. And finally, the primary
19 efficacy assessment of psychotic symptoms should be
20 performed by independent, centralized raters.

21 We reviewed these learnings with the agency
22 and designed study 020 as follows. Potential study

1 patients were assessed using Neuropsychiatric
2 Inventory or NPI. Patients who met entry criteria
3 received brief psychosocial therapy during the
4 2-week screening period. At baseline, the severity
5 of psychotic symptoms was measured using Scale for
6 Assessment of Positive Symptoms Parkinson's Disease
7 version, or SAPS-PD.

8 Patients who met entry criteria were
9 randomized to 34-milligram pimavanserin or placebo
10 for the 6-week treatment period. Study assessments
11 were performed at week 2, 4, and 6. All patients
12 completing the study were offered the opportunity
13 to roll into study 015, an open-label safety
14 extension study.

15 The key inclusion criteria for study 020
16 were designed to ensure that patients would have an
17 established diagnosis of PD psychosis and symptoms
18 severe enough to require pharmacologic treatment.
19 To ensure sufficient severity of symptoms, criteria
20 from both NPI at initial screening and SAPS-PD at
21 time of randomization needed to be met. All these
22 requirements were designed to establish a minimum

1 of moderate severity of the disease. Study
2 patients were required to be on a stable PD
3 medication.

4 In terms of exclusion criteria, patients
5 needed to have PD-associated psychosis, not any
6 other type, and were not allowed to use any other
7 antipsychotic medications. Additionally, patients
8 with moderate or severe dementia, meaning those
9 with Mini-Mental Status Exam score or less than 21,
10 were not included in the study.

11 The endpoints in study 020 were selected to
12 provide a broad range of perspectives on the
13 efficacy of pimavanserin. The primary endpoint was
14 SAPS-PD. This is a shorter version of the 20 items
15 SAPS H plus D. SAPS-PD is a 9-item scale that
16 focuses on the most frequently reported items of
17 the SAPS H plus D as determined from the
18 pretreatment assessments of the PD psychosis
19 patients in four prior clozapine and pimavanserin
20 clinical trials. SAPS-PD assessment in the
21 study 020 was conducted by the centralized
22 independent raters via live video feed.

1 Secondary endpoints included Clinical Global
2 Impression Severity and Improvement scale or CGI-S
3 and CGI-I. These were rated by the treating
4 clinician at the site.

5 Exploratory endpoints consisted of the Zarit
6 Caregiver Burden Scale, which was completed by the
7 primary caregiver, and the Scale for Outcomes in
8 Parkinson's disease, SCOPA, sleep module, which
9 captured the patient's experience of nighttime
10 sleep and daytime sleepiness.

11 We randomized 199 patients in the study 020.
12 The boxes in the middle show the modified intent to
13 treat population, mITT, which was the primary
14 efficacy analysis population. Over the study
15 duration, 16 patients from the pimavanserin
16 treatment arm discontinued prematurely. In the
17 placebo group, 7 patients discontinued prior to
18 study completion.

19 At the bottom of the graph, we see that the
20 majority of patients completed 6 weeks in both
21 treatment arms, 89 patients or 85 percent in the
22 pimavanserin group, and 87 or 93 percent in the

1 placebo group.

2 Baseline demographics of the two treatment
3 arms were generally well matched. Patient mean age
4 was 73. About half of the patients were between 65
5 and 75 years old with approximately one-third of
6 the patients over 75. The gender distribution
7 generally reflects the Parkinson's disease
8 population with a somewhat higher proportion of
9 male subjects in the pimavanserin group.

10 Baseline disease characteristics were also
11 similar between the two groups. In general,
12 patients enrolled were experiencing moderately
13 severe psychotic symptoms. As one would expect,
14 study 020 enrolled an advanced PD population.
15 Subjects had Parkinson's disease for about 10 years
16 and psychosis for over 30 months. The described
17 baseline demographics and disease characteristics
18 are consistent with the previous PDP studies and
19 with the general population of PD psychosis
20 patients.

21 I will now present the results of study 020.
22 For the primary endpoint, change from baseline in

1 the SAPS-PD score, the pimavanserin treatment arm
2 achieved a mean improvement of 5.8 versus 2.7 for
3 placebo. This is a statistically significant
4 difference with a p-value of 0.001. The observed
5 difference between the two groups at week 6 was
6 3.06.

7 Both arms showed equal improvement at
8 week 2, but by the week 4, statistical separation
9 had been reached, And the gap between 34-milligram
10 pimavanserin arm and placebo continued to grow
11 through the week 6 endpoint.

12 The question could be asked, would the
13 results be any different if the larger SAPS
14 H plus D scale was used? As the full 20 items
15 SAPS H plus D scale was assessed in the study, we
16 conducted this analysis. The results were
17 essentially the same on both scales. Using SAPS
18 H plus D total score, pimavanserin arm achieved a
19 mean improvement of 6.5 versus 3.1 for placebo.
20 The difference between the two arms at week 6 was
21 3.4 points, almost identical to the primary
22 analysis with SAPS-PD.

1 Additional sensitivity analysis assessed the
2 impact of missing data on the primary SAPS-PD
3 endpoint and provided evidence of a highly
4 consistent effect regardless of assumptions. In
5 this graph, each line displays the estimated
6 treatment difference between pimavanserin and
7 placebo at week 6 and 95 percent confidence
8 interval.

9 The top two lines show the results from the
10 primary MMRM and LOCF analysis in the mITT
11 population. The bottom three analyses utilize data
12 from the all randomized population under different
13 assumptions: 1, worst or baseline observation
14 carried forward; 2, multiple imputation analysis
15 under assumption that missing values are missing at
16 random; and 3, pattern mixture model which assumes
17 that after withdrawal, subjects in the pimavanserin
18 arm follow the same trajectory as subjects in the
19 placebo arm.

20 As you can see, all of these analyses show
21 the significant improvement in psychosis for
22 pimavanserin over placebo. Therefore, we conclude

1 that the primary analysis results were not impacted
2 by the dropouts or missing data.

3 Another way to evaluate treatment effect is
4 by responder analysis. This graphic shows the
5 proportion of responders for pimavanserin
6 34 milligram and placebo, where responders are
7 defined as having achieved a given threshold of
8 SAPS-PD reduction, 10 points, 7 points and so on.

9 Note that in all comparisons regardless of
10 the responder definition, a notably larger and
11 statistically significant proportion of
12 pimavanserin-treated patients was observed. Over
13 65 percent of patients in the pimavanserin arm
14 experienced more than 3-point improvement compared
15 to 42 percent in the placebo arm. Using higher
16 thresholds of over more than 5 points, or more than
17 7-point improvement on the SAPS-PD scale, a
18 significantly larger proportion of patients on
19 pimavanserin, 54 and 41 percent respectively,
20 experienced this level of improvement compared to
21 33 and 27 percent in the placebo group.

22 Even more striking was the proportion of

1 patients with the highest possible response,
2 meaning patients who achieved 100 percent reduction
3 in the SAPS-PD total score. Fourteen percent of
4 pimavanserin-treated patients achieved complete
5 remission of their psychotic symptoms. This
6 compares to only 1 percent of placebo patients.

7 The secondary endpoints in study 020 are
8 also supportive of efficacy. Clinical Global
9 Impression scales provided assessment of both
10 severity and improvement of overall psychotic
11 symptoms from the perspective of a treating
12 clinician at a site. The results were consistent
13 with the observations on the primary endpoint. For
14 the CGI-S, overall severity shown on the left,
15 pimavanserin showed a significant improvement over
16 placebo at both week 4 and week 6. The CGI-I,
17 overall improvement presented on the right, also
18 demonstrated significant superiority of
19 pimavanserin over placebo.

20 Another way to examine CGI efficacy data is
21 to look at the categorical response. We present
22 here the proportion of patients in each individual

1 category of CGI improvement ranging from very much
2 improved on the far left to very much worse on the
3 far right with no change in the middle of this
4 graph. We observe a clear shift to the left,
5 meaning in the direction of improvement in the
6 pimavanserin-treated group.

7 Statistical tests of this shift revealed
8 significance. Notably, a substantively larger
9 proportion of patients was seen in the much
10 improved and very much improved categories. A
11 total of 45 percent of pimavanserin-treated
12 patients experienced this meaningful level of
13 clinical improvement.

14 SAPS-PD and CGI both demonstrate clinical
15 improvement. I'm emphasizing this because these
16 two ratings were performed by two independent
17 observers. Specifically, in the case of SAPS-PD, a
18 central rater blinded for all other assessments,
19 prior ratings, or study visit number, assessed
20 psychotic symptoms. And for CGI, the assessment
21 was performed by the treating clinician at the site
22 who evaluated patient symptoms while blinded for

1 the SAPS-PD score.

2 We see a strong and statistically
3 significant correlation between the two independent
4 measures of change in psychotic symptoms. In other
5 words, the clinician's ratings strongly corroborate
6 the changes in the SAPS-PD scale rated by the
7 independent central rater.

8 PD psychosis affects patients, but it also
9 impacts their family, particularly those who
10 provide immediate care for the patient. The
11 efficacy of pimavanserin is further supported by
12 the caregiver's own assessment of how the patient's
13 condition affects them personally. We assess this
14 with the 22-item Zarit Caregiver Burden Scale. The
15 results demonstrated significant improvement over
16 placebo at week 6.

17 Sleep disturbance is a very common complaint
18 in the PD psychosis and can exacerbate psychotic
19 symptoms or worsen cognitive functioning. The
20 ability to improve sleep would represent an
21 important additional clinical benefit to patients.

22 In study 020, there was significant

1 improvements in the SCOPA nighttime score, shown on
2 the left, as a decrease in nighttime sleep
3 disturbance. This was accompanied by a significant
4 reduction in daytime sleepiness, shown on the
5 right.

6 The UPDRS was included in the study as the
7 key secondary endpoint designed to provide an
8 assessment of pimavanserin impact on motor
9 function. We present here that comparison of
10 pimavanserin versus placebo on the combined UPDRS
11 Parts II and III score. We saw equal effects
12 between study arms, both showing a small
13 improvement from baseline.

14 Similar to what was seen in all previous
15 pimavanserin studies, these results demonstrate
16 that there was no appreciable difference between
17 pimavanserin and placebo. The observed differences
18 were well within the prospectively defined non-
19 inferiority margin of five points. Based on this
20 data, we conclude that pimavanserin does not worsen
21 motor symptoms in Parkinson's patients.

22 I will now show available efficacy data from

1 the ongoing open-label extension study, study 015.
2 All patients rolling into study 015 from study 020
3 underwent a SAPS assessment at week 10, which was
4 4 weeks following completion of the earlier
5 placebo-controlled study. This assessment employed
6 the same real-time video feed used in study 020,
7 and importantly, both the raters and patients were
8 blinded to the previous study randomization.

9 As shown in the solid blue line, those
10 patients previously on 34-milligram pimavanserin
11 arm maintained their SAPS-PD improvement during the
12 first 4 weeks of open-label active treatment.
13 Those patients who had received placebo in the
14 double-blind study, shown in the dashed blue line,
15 caught up to the pimavanserin group from the
16 double-blind study, achieving a reduction from
17 their 6 weeks' baseline, replicating the change
18 seen with the active treatment in study 020.

19 As presented earlier, we identified 13 out
20 of 95 pimavanserin patients that experienced
21 complete remission of psychotic symptoms during the
22 6 weeks treatment. We followed these 13

1 pimavanserin SAPS-PD complete responders and their
2 CGI-S score into the open-label extension study.
3 We used CGI-S because SAPS-PD was not captured
4 continuously in the extension study.

5 The results are encouraging. At the end of
6 one year of treatment, 11 out of 13 complete
7 responders were continuing on treatment. The
8 average severity of their symptoms was assessed as
9 borderline ill, a level essentially unchanged from
10 their average severity after the first 6 weeks of
11 double-blind study.

12 There is a remarkable consistency across the
13 multiple prespecified efficacy endpoints and
14 sensitivity analysis, demonstrating positive
15 results for the pimavanserin 34-milligram dose.
16 Results of these analyses are tabulated here
17 showing the measure, least square mean of the
18 treatment change, the effect size using Cohen d,
19 and the unadjusted p-value.

20 The observed effect size for the primary and
21 secondary efficacy measures was consistently around
22 .5, in the upper range of what is seen with

1 antipsychotics in schizophrenia, for instance.

2 In 9 out of 10 prespecified outcomes, the
3 34-milligram pimavanserin treatment provided
4 clinically and statistically significant superior
5 results compared to placebo. This effect size and
6 the consistent demonstration of efficacy across
7 multiple measures and by multiple assessors
8 presents a strong and convincing argument for the
9 consistency, robustness, and clinical relevance of
10 the pimavanserin treatment benefit.

11 Cohen d effect size is a measure often used
12 to compare efficacy of different drugs across
13 trials. We wanted to compare pimavanserin to other
14 antipsychotics. We used published data from the
15 schizophrenia trials.

16 Leucht published in his 2013 paper
17 comparative effectiveness for 15 typical and
18 atypical antipsychotics in schizophrenia. Using
19 the same methodology of standardized mean
20 difference, we determined the effect size for
21 pimavanserin in PD psychosis to be at .5 both when
22 change in SAPS-PD is used or when CGI-S or CGI-I

1 were used.

2 As you can see, pimavanserin effect size in
3 PD psychosis compares favorably to effect size
4 reported for most antipsychotics from schizophrenia
5 studies. The reason we use schizophrenia studies
6 for this illustration is simple: no similar
7 comparison or effect size from PD psychosis was
8 possible as almost all antipsychotics tested,
9 namely, quetiapine and olanzapine, failed to
10 demonstrate superiority over placebo. The only
11 other antipsychotic that established efficacy in PD
12 psychosis was clozapine, suggesting how difficult
13 it can be to demonstrate efficacy in this complex
14 condition.

15 The number needed to treat, NNT, is another
16 measure used to communicate the clinical
17 effectiveness of treatment. We calculated NNT for
18 the previously presented pimavanserin increasing
19 levels of response. Here are the NNTs for several
20 improvement cutoffs, 3, 5, 7, 10 points on the
21 SAPS-PD scale, also, 100 percent response on the
22 SAPS-PD scale, and finally, much or very much

1 improved on the CGI-I or Clinical Global
2 Assessment.

3 Two important observations here: for the
4 clinical outcome of much improved and very much
5 improved, we calculated NNT of 5. And for the
6 ultimate treatment success of complete symptom
7 remission, we observed the NNT of 8, estimating
8 that for every 8 patients treated with
9 pimavanserin, one patient will experience full
10 remission of psychotic symptoms.

11 In conclusion, the totality of data from the
12 clinical program demonstrates that pimavanserin at
13 once daily dose of 34 milligrams is an effective
14 treatment for psychotic symptoms in Parkinson's
15 disease. Study 020 provides the primary evidence
16 for this conclusion.

17 We observed substantive proportion of
18 patients experiencing higher categories of
19 response, consistent and meaningful decrease in
20 average severity of psychotic symptoms on both
21 SAPS-PD and CGI, persuasive statistical evidence,
22 substantial effect size, low NNTs, and multiple

1 confirmatory sensitivity analysis. Notably, the
2 antipsychotic benefit of pimavanserin was achieved
3 without negative impact on motor function.

4 I would like now to introduce Dr. George
5 Demos, executive director of drug safety and
6 pharmacovigilance at Acadia, who will present the
7 safety data for pimavanserin.

8 **Applicant Presentation - George Demos**

9 DR. DEMOS: Thank you, Dr. Stankovic.

10 Good morning, everyone. The majority of the
11 safety data we'll be reviewing this morning were
12 generated by studies in Parkinson's disease
13 patients with psychosis, a condition which occurs
14 later in the course of Parkinson's disease. The
15 study population is therefore elderly and
16 frequently frail with an underlying progressive
17 neurodegenerative disease, the impacts of which
18 Dr. Isaacson outlined earlier.

19 I'll begin with the safety data obtained in
20 the phase 3 studies, which are comprised of
21 double-blind, controlled 6-week studies 012, 014,
22 and 020. Doses here included 8.5, 17, and

1 34 milligrams of pimavanserin and placebo. We'll
2 review the overall adverse event profile and focus
3 on deaths, serious adverse events and
4 discontinuations. I'll then briefly review open-
5 label safety and adverse events and topics of
6 special interest.

7 In addition to the challenges and risks from
8 their Parkinson's disease, the subjects in these
9 studies carry overall risks associated with aging,
10 including multiple cardiac risk factors such as
11 hypertension, hyperlipidemia, and coronary-related
12 heart disease with most of them on multiple
13 concomitant medications. At baseline, the average
14 age of these subjects was 71 years. Duration of
15 Parkinson's disease psychosis was 26 months, and
16 baseline UPDRS Parts II and III were 52.

17 Over 40 percent had two or more
18 cardiovascular-related risk factors, and 50 percent
19 were taking five or more non-Parkinson's disease
20 concomitant medications.

21 A total of 25 studies have been conducted in
22 the evaluation of pimavanserin with over 1200

1 people exposed, over 1,000 of which participated in
2 controlled or extension studies, including 616
3 Parkinson's disease patients with psychosis.
4 Seventy percent of subjects have received
5 once-daily 34-milligram doses or higher over an
6 extended period, representing more than 900
7 patient-years of therapeutic experience at this
8 dose.

9 Overall, treatment-emergent adverse events
10 were reported at numerically similar rates across
11 the different arms. In the 34-milligram arm,
12 approximately 8 percent of subjects discontinued
13 compared to 4 percent in placebo, and 8 percent of
14 subjects reported serious adverse events versus
15 3.5 percent in placebo. There were 3 deaths on
16 34 milligrams, one death on 8.5 milligrams, and one
17 in placebo.

18 As we'll soon see, there is considerable
19 overlap, and several of these discontinuations,
20 serious adverse events, and deaths refer to the
21 same subjects. I'll now focus on the 34-milligram
22 dose and the adverse events that occurred in at

1 least 5 percent of those subjects.

2 The overall event rates were comparable
3 between pimavanserin and placebo at about
4 61 percent. Urinary tract infection rates were
5 reported evenly in both arms at about 7 percent.
6 Events occurring with a 2 percent or greater
7 difference in the pimavanserin arm versus placebo
8 were nausea, peripheral edema, confusion, and
9 hallucination.

10 Events occurring with a 2 percent or greater
11 difference in the placebo arm versus pimavanserin
12 were falls, headache, and orthostatic hypotension.
13 Falls and orthostatic hypotension are of particular
14 interest as they are problematic with potentially
15 serious consequences in this population.

16 In the PDP 6 double-blind studies, there
17 were 5 deaths, and I'd like to briefly describe
18 these for you. Beginning with the subject
19 randomized to placebo, this is an 85-year-old male
20 with relevant history of hypertension and atrial
21 fibrillation, and on day 13 was found staring into
22 space but unresponsive.

1 The symptoms resolved by the time he arrived
2 at the emergency department, and he was diagnosed
3 with a transient ischemic attack. MRI of the brain
4 revealed diffuse, small vessel ischemic changes and
5 parenchymal volume loss, and a swallow study
6 indicated dysphagia. On day 27, study drug was
7 discontinued due to an unspecified cardiac
8 arrhythmia on top of his atrial fibrillation.

9 The subject slowly improved, and he was
10 transferred to the rehab unit, where on day 36, he
11 collapsed during occupational therapy in cardiac
12 arrest. Resuscitative efforts were unsuccessful.

13 For the subjects randomized to pimavanserin,
14 the first is a 61-year-old male on 8.5 milligrams
15 with no reported medical history or concomitant
16 medications who had not been responding to family.
17 His son asked police to open the subject's house,
18 where he was found in bed deceased. Foul play and
19 suicide were ruled out. And though no autopsy was
20 performed, the coroner ruled the death a myocardial
21 infarction. By presentation, however, sudden death
22 or cardiac arrest are more likely. ECGs obtained

1 at screening, baseline and days 10, 20, and 38
2 showed no change in the QTC interval.

3 The next subject reported as respiratory
4 distress is an 84-year-old female with history of
5 orthostatic hypotension and depression.

6 Pimavanserin was discontinued about a month after
7 randomization, 4 days prior to her admission for
8 cataract surgery. Postoperatively, she was
9 fatigued and never regained full alertness.

10 An unspecified elevation of the white blood
11 cells was reported, and she had a fever of 101.8.

12 The following day, she was described as having
13 hypoventilation of the right lung, and she was
14 started on antibiotics and oxygen. Two days later,
15 a chest x-ray revealed left lung atelectasis, and
16 she was intubated. And 2 weeks after that, a
17 tracheotomy was performed. But her respiratory
18 status declined, and she died on day 61, 32 days
19 post her last dose of pimavanserin.

20 The next subject, reported as sepsis, was a
21 74-year-old male with history of hyperlipidemia and
22 recurrent generalized dermatitis. He had an

1 elevated white blood cell count, an eosinophilia of
2 29 percent at baseline. On day 16, he was treated
3 with a short course of steroids, and on day 38, he
4 presented to the emergency department with a
5 continuing rash, mental status changes described as
6 paranoid and delusional, confused and agitated, and
7 bilateral lower extremity edema.

8 He was admitted with psychotic disorder.
9 Two days later, he was diagnosed with bilateral
10 pneumonia and urinary tract infection with blood
11 cultures positive for staph aureus. He was treated
12 with broad-spectrum antibiotics, but following
13 discussion with the family, comfort care measures
14 were instituted, and the subject died on day 45.

15 The last subject, reported as septic shock,
16 is a 76-year-old male with history of multiple
17 episodes of pneumonia who became restless and
18 confused with difficulty sleeping on day 4 and was
19 admitted to hospital. Diagnostic assessments to
20 rule out causes of acute confusion were negative.

21 Because his wife could not care for him, he
22 was discharged to a nursing home despite not having

1 returned to baseline. Two days later, he was
2 readmitted with low grade fever and general decline
3 with hypotension, decreased consciousness, and
4 found to have a leukocytosis, acute renal failure,
5 and a chest x-ray suggesting aspiration pneumonia.

6 As the subject's condition was considered
7 critical and in accordance with the family's
8 request, medical treatment was discontinued, and he
9 was provided with comfort measures only. The
10 subject died the next day on day 10.

11 To summarize, the three deaths in the
12 34-milligram group included a male with baseline
13 dermatitis, leukocytosis, and eosinophilia treated
14 with steroids and succumbing to infection; a male
15 admitted with mental status change considered due
16 to infection succumbing to complications of
17 pneumonia; and a female who developed respiratory
18 complications following cataract surgery who had
19 presumably been well enough to undergo that
20 elective surgery. In two of these deaths, medical
21 measures were discontinued at the request of
22 families.

1 I would now like to present the remaining 13
2 subjects on 34 milligrams as well as all PDP 6
3 placebo subjects reporting serious adverse events.
4 These events met the regulatory definition of
5 seriousness because the subjects were either
6 hospitalized or considered to have disability.

7 Based on medical review, we broadly
8 categorized them as events that occurred
9 substantially after treatment discontinuation,
10 events reasonably likely to be present at baseline
11 with past medical history, events with evidence
12 suggestive of alternative etiology, and those with
13 no alternative etiologies identified for either
14 pimavanserin or placebo subjects.

15 The first category includes one report of an
16 event following treatment discontinuation in a
17 subject on the pimavanserin arm. The subject is an
18 80-year-old female who discontinued study drug on
19 day 15 and was started on quetiapine. On day 36,
20 25 days post her last dose of pimavanserin, she was
21 hospitalized with cold-like symptoms and diagnosed
22 with bronchitis.

1 The next category includes 4 subjects on
2 drug and none on placebo who had evidence of the
3 event present at baseline. These include a breast
4 cancer reported in a 77-year-old who had a routine
5 mammogram during her screening period, positive
6 biopsy on day 20, and a mastectomy resulting in
7 discontinuation on day 32.

8 It also includes a subject with a urinary
9 tract infection on day 8 who had 6 to 25 white
10 cells in her urine at baseline. She developed
11 symptoms of infection with a urine culture
12 indication 2 species of oral antibiotic resistant
13 bacteria. She had just completed treatment for UTI
14 6 weeks prior to randomization.

15 The next category includes those subjects
16 with clinical evidence of alternative etiology for
17 the events with 5 subjects in the pimavanserin arm
18 and 7 in placebo. An example in the pimavanserin
19 arm is a 72-year-old female with chronic atrial
20 fibrillation hospitalized for pacemaker placement
21 following an episode of syncope. And in the
22 placebo arm, a 73-year-old male who experienced

1 mental status changes following placement in
2 respite care due to hospitalization of his
3 caregiver spouse who needed surgery.

4 The last category includes two subjects on
5 pimavanserin, both of whom described vivid
6 hallucinations following randomization and were
7 hospitalized for workup. Both subjects were
8 discontinued and started on alternative
9 antipsychotics.

10 Of the 13 subjects in the pimavanserin arm,
11 5 remained on study drug with no further adverse
12 events reported.

13 The imbalance in the frequency of serious
14 adverse events did prompt us to carefully review
15 each case in an attempt to try to understand
16 whether there is some contribution of pimavanserin
17 to these events. There were more urinary tract
18 infections reported as serious, but there was no
19 difference between pimavanserin and placebo in the
20 overall urinary tract infection rate. There does
21 not appear to be a common mechanism or etiology
22 that explains the imbalance in serious adverse

1 events.

2 Listed here are the events that led to study
3 discontinuation, the most common being
4 hallucination, psychotic disorder, urinary tract
5 infection, and fatigue. Of the four hallucination
6 discontinuations, two were previously shown adverse
7 events. Two of the three psychotic disorders were
8 also reported as serious adverse events, a
9 constellation of symptoms indicating infection in
10 the two subjects we just reviewed as the sepsis and
11 septic shock-related deaths.

12 The two urinary tract infections were also
13 serious adverse events considered to have clinical
14 evidence of preexistence to study drug
15 administration, and one of the reports of fatigue
16 was in conjunction with the aforementioned urinary
17 tract infection.

18 The overall discontinuation rate is
19 relatively low compared to similar studies with
20 other antipsychotics. Adverse events leading to
21 discontinuation are recognized as an acceptable
22 variable in calculating numbers needed to harm.

1 We respectfully disagree with the agency's
2 calculation of numbers needed to harm, which
3 included subjects with serious adverse events who
4 continued on pimavanserin as we've just seen but
5 experience no further adverse events.

6 Let's turn our attention to the long-term
7 open-label safety data. Open-label extension
8 study 010 started in 2004 and rolled into study
9 015, which began in 2007 and is ongoing today. The
10 open-label program intended to capture safety
11 information from subjects allowed to remain on
12 therapy for as long as the investigator considered
13 them to be deriving benefit.

14 The subjects continued in the study even
15 after they were placed in hospice or became bed
16 bound and could no longer meet study requirements
17 such as orthostatic measurements or collecting
18 urine for urinalysis.

19 Four hundred ninety-eight subjects rolled
20 over into the open-label extension with a median
21 time on treatment of over 15 months. Over 170
22 patients received drug for over 2 years for a total

1 of more than 900 years of patient exposure. The
2 person with the longest exposure has been on
3 pimavanserin for over 10 years.

4 Eighty-five percent of subjects have
5 reported an adverse event with the most common
6 being falls, urinary tract infections,
7 hallucinations, decreased weight, confusion, and
8 constipation, each reported in 10 percent or more
9 of the subjects. The majority of these events have
10 been mild or moderate in severity, and advancing
11 age was the only clear predictor for those adverse
12 events, particularly in patients who are over 80.
13 There does not appear to be a temporal pattern
14 associated with these events, and no new signals
15 have been identified with prolonged exposure.

16 Thirty-nine percent of subjects in the
17 long-term study have experienced at least one
18 serious adverse event. The most common have been
19 pneumonia and urinary tract infections reported by
20 3.6 and 3.2 percent of subjects, followed by hip
21 fracture and aspiration pneumonia.

22 Sixty-two deaths have been reported over the

1 long follow-up period with the most common events
2 mapping to the cardiac, respiratory, and nervous
3 system disorders. The events reported in the
4 long-term safety study are representative of the
5 comorbidities in an elderly PDP population. The
6 nature of these events appeared within expectations
7 for this population.

8 As we have noted, there is an imbalance in
9 serious adverse event and mortality in the current
10 pimavanserin database, and similarity to the
11 experience with other antipsychotic drugs in this
12 regard has been described by the agency. We are
13 committed to investigate this imbalance further and
14 specifically to increase the body of evidence that
15 is available to inform us on this question.

16 Our efforts begin with diligent
17 pharmacovigilance, with detailed follow-up of
18 serious adverse events and fatalities in patients
19 treated with pimavanserin. Our ongoing and planned
20 clinical trial development program for pimavanserin
21 includes additional randomized placebo-controlled
22 trials in additional indications.

1 While one randomized trial may not be
2 sufficient to detect a clinically significant
3 signal, we will have the ability to pool our safety
4 data across several clinical trials. In aggregate,
5 we expect that this will be the largest controlled
6 clinical trial database of its kind.

7 We have commissioned a large epidemiological
8 investigation of patients with Parkinson's disease
9 psychosis, utilizing the complete Medicare database
10 to identify a comparable cohort of patients and
11 allow uncontrolled safety data to be considered in
12 the context of the natural history of Parkinson's
13 disease psychosis.

14 We are in the process of designing a large,
15 nonrandomized, observational study of this
16 population intended to include patients treated
17 with marketed pimavanserin as well as with
18 alternative therapies.

19 Finally, we are exploring opportunities to
20 participate in hypothesis-testing analyses of
21 contemporary healthcare databases, consulting with
22 pharmacoepidemiologists with expertise in designing

1 prospective safety analyses in such databases as
2 well as other approaches.

3 Overall, we expect these measures will
4 greatly add to our understanding of the natural
5 history of psychosis in the elderly and of the
6 appropriate use of pimavanserin and potentially
7 other antipsychotic agents in this population.

8 To complete the safety presentation, I will
9 review topics and events of special interest shown
10 here. We focused on topics based broadly on the
11 potential pimavanserin pharmacology or known
12 pharmacodynamic effects such as drug-drug
13 interactions and the effect on the QT interval.
14 And we also examined the risks associated with
15 class effects of the atypical antipsychotics.

16 Dopaminergic agents are central to treating
17 Parkinson's disease symptoms with the most commonly
18 prescribed medicines being carbidopa/levodopa
19 combinations. To evaluate any potential
20 interactions, we studied Sinemet with pimavanserin,
21 which showed that pimavanserin had no effect on
22 levodopa exposure.

1 Pimavanserin is metabolized by CYP3A4 but
2 has not been shown to be an inducer or inhibitor of
3 CYP3A4, using midazolam, a sensitive probe drug.
4 Inhibition of CYP3A4 with a potent inhibitor
5 increased plasma concentration of pimavanserin
6 threefold, and we will be recommending a 50 percent
7 reduction in dose in labeling.

8 The effects of pimavanserin were examined in
9 a thorough QT study in healthy volunteers as well
10 as in the phase 3 randomized controlled studies.
11 In the phase 3 studies, maximal mean change for the
12 34-milligram dose was 6.9 milliseconds with the
13 upper 90 percent confidence interval being
14 10 milliseconds. Most importantly, there were no
15 meaningful outliers in the 34-milligram dose
16 compared to placebo.

17 Current atypical antipsychotics known risks
18 for significant side effects include worsening of
19 Parkinsonism, orthostasis, sedation, metabolic
20 disorders, and blood dyscrasias. Pimavanserin
21 safety data was analyzed with these in mind, and
22 I'll now highlight some of these findings.

1 With respect to cerebral vascular accidents,
2 there were no strokes or related events reported in
3 the double-blind studies, and in the open-label
4 extension, the event rate of cardiovascular
5 accidents was 1.1 per 100 patient-years, which is
6 what would be expected in this age population.

7 Orthostatic hypotension is a major concern
8 for Parkinson's disease patients resulting in
9 syncope or falls and injuries. Subjects randomized
10 to placebo reported or met vital sign criteria for
11 orthostatic hypotension at a much higher rate
12 compared to pimavanserin.

13 Sedation, another known side effect of
14 current antipsychotics, can contribute to falls and
15 urinary tract infections. Sedation and related
16 events, including somnolence and lethargy, were
17 balanced between pimavanserin and placebo. There
18 were no reports of sedation in the double-blind
19 studies, and somnolence was reported at the same
20 rate between the arms.

21 Metabolic disorders include effects on blood
22 sugar and body weights. Adverse events indicating

1 hyperglycemia were balanced between placebo and
2 pimavanserin. Mean changes in random glucose
3 levels from baseline were also similar between the
4 arms. Weight gain is a known side effect of
5 current antipsychotics. However, the mean change
6 in weight from baseline in both placebo and
7 pimavanserin groups was negligible.

8 Leukopenia and in particular neutropenia is
9 an important consideration in choosing an
10 antipsychotic. Pimavanserin has shown no effects
11 on blood analytes, and in particular, no effect on
12 the absolute neutrophil count.

13 Motor tolerability was of particular
14 interest in this already compromised patient
15 population due to the concern with current
16 antipsychotics and their inherent antagonism of
17 dopamine receptors. In fact, for this reason, FDA
18 required the motoric control be measured as a key
19 secondary endpoint in all phase 3 studies.

20 As the figure shows, across multiple
21 placebo-controlled studies, pimavanserin has not
22 been associated with any impairment in motoric

1 control. A non-inferiority to placebo has been
2 established. As such, the efficacy seen with
3 pimavanserin has not come at the expense of
4 worsening Parkinsonism.

5 In summary, across multiple studies,
6 pimavanserin was well tolerated, and the safety
7 profile was compatible with both short- and
8 long-term therapy in patients with Parkinson's
9 disease psychosis. In the double-blind studies,
10 treatment emergent events were numerically similar
11 to placebo, but there were more discontinuations,
12 serious adverse events, and deaths observed in the
13 34-milligram dose group.

14 These events were few, and review of the
15 cases demonstrated causal association with
16 pimavanserin is difficult to ascertain with no
17 unifying pathophysiologic mechanism. This
18 population is particularly challenged due to their
19 underlying progressive neurodegenerative disease as
20 well as their advanced age. Subjects have
21 increased risk for many diseases, reflected in the
22 events reported, including respiratory and

1 cardiovascular disease.

2 Modest increases in the QTC can be managed
3 through information provided to physicians similar
4 to other medicines with similar degree of QT
5 prolongation, and this language has been proposed
6 in draft labeling.

7 In contrast to the adverse effects seen with
8 current antipsychotics, the safety profile with
9 pimavanserin is distinctly different. Major
10 concern such as sedation, blood dyscrasias, and in
11 particular motor control effects have not been
12 observed with pimavanserin, which would offer
13 physicians an acceptable alternative for treating
14 this vulnerable population.

15 In conclusion, pimavanserin is appropriate
16 for short- and long-term treatment of PDP with a
17 risk profile that has been characterized and is
18 manageable.

19 I would now like to invite Dr. Stankovic to
20 address the risk/benefit profile of pimavanserin.

21 **Applicant Presentation - Serge Stankovic**

22 DR. STANKOVIC: I would like to put the

1 overall benefit/risk profile of pimavanserin in the
2 context of the disease and antipsychotic treatments
3 currently used off label.

4 Parkinson's disease psychosis is a serious
5 progressive disorder. The onset of psychosis is a
6 turning point in the course of illness that
7 dramatically increases the profound burden of
8 advanced PD. Dr. Isaacson described the difficult
9 choices that have to be made when using currently
10 available antipsychotics off label.

11 Most of the antipsychotics have not
12 demonstrated efficacy in controlled studies and
13 cause worsening of motor symptoms. Some are rarely
14 used due to serious safety and tolerability
15 concerns or extensive monitoring requirements.

16 If left untreated, on the other hand, the
17 consequences of PD psychosis are even more
18 troubling. As presented earlier, the occurrence of
19 psychotic symptoms often signals accelerated
20 disease progression, and if untreated, will lead to
21 ultimate deterioration. The need for a PD
22 psychosis treatment is clear.

1 With its highly targeted and selected
2 receptor binding profile, pimavanserin provides an
3 alternative approach to the treatment of psychosis
4 in Parkinson's patients. This is the first
5 antipsychotic to establish efficacy in PD psychosis
6 without dopamine blockade.

7 The totality of data from the pimavanserin
8 development program has consistently demonstrated
9 benefit to patients and their caregivers. In
10 addition to meaningful average reduction in
11 severity of symptoms, a significant proportion of
12 patients experience a noteworthy improvement or a
13 complete remission of their psychotic symptoms.
14 This was accompanied by a reduction in caregivers'
15 burden and improvement in patients' sleep and
16 daytime wakefulness.

17 The benefit of pimavanserin as treatment for
18 PD psychosis is also reflected in the absence of a
19 number of safety liabilities seen with currently
20 used antipsychotics. We demonstrated that
21 pimavanserin does not affect motor symptoms. This
22 makes it particularly suitable for patients

1 requiring dopaminergic therapy.

2 In addition, we did not observe any increase
3 in the risk for occurrence of orthostatic
4 hypotension, falls, sedation, metabolic, or blood
5 alterations, all of which are known safety concerns
6 with other antipsychotics.

7 The safety profile of pimavanserin is
8 characterized in the largest development program
9 conducted in PD psychosis patients. In the 6-week
10 controlled trials, we observed a higher number of
11 serious adverse events and deaths. The small
12 number of reported events makes it difficult to
13 reliably assess an association with treatment.

14 Our review of these events did not reveal
15 any obvious unifying pathophysiologic process or
16 unique adverse event that drives or dominates this
17 disproportion. The events were consistent with the
18 risk factors associated with background disease and
19 medical comorbidities. However, the seriousness of
20 these events requires continued focus and further
21 evaluation through postmarketing vigilance.

22 Modest QT prolongation was observed with

1 pimavanserin. We consider this risk manageable and
2 propose appropriate precautions. Metabolism of
3 pimavanserin is affected by strong CYP3A4
4 inhibitors. Therefore, when prescribed with potent
5 CYP3A4 inhibitors, a reduction of pimavanserin dose
6 is recommended.

7 Acadia Pharmaceuticals outlined the case for
8 pimavanserin as a breakthrough treatment,
9 demonstrating substantial improvement over existing
10 off-label treatment options. We presented the
11 evidence for meaningful benefit of pimavanserin
12 therapy that matters to patients and caregivers.
13 Clinically relevant improvements were observed
14 across multiple measures of psychosis and without
15 adverse effect on motor function.

16 The safety profile of pimavanserin is
17 adequately characterized and risks are manageable.
18 In conclusion, the totality of data supports the
19 assessment of the overall positive benefit/risk
20 profile for pimavanserin.

21 This concludes our data presentation. I
22 would like to introduce Professor Clive Ballard

1 from the Institute of Psychiatry at King's College
2 London, who will provide a clinical perspective on
3 the utility of pimavanserin for the treatment of
4 Parkinson's disease psychosis.

5 **Applicant Presentation - Clive Ballard**

6 DR. BALLARD: Thank you.

7 Good morning. I'm Clive Ballard, an
8 academic old age psychiatrist from London in the
9 U.K. As a clinician, I regularly see people with
10 Parkinson's disease and those with related
11 dementias and psychosis. I've also undertaken
12 numerous clinical trials, focusing on the treatment
13 of psychiatric symptoms in people with
14 neurodegenerative diseases, including studies
15 evaluating the benefits and harms of
16 antipsychotics, and I have conducted systematic
17 reviews and meta-analyses focusing on antipsychotic
18 drugs in these conditions.

19 Acadia has compensated me for my work with
20 them, but I do not have a financial interest in the
21 outcome of today's meeting.

22 I am to give a clinical perspective of

1 treatment issues based on my experience as a
2 clinician, researcher, and clinical trialist to
3 provide additional context to the presentations
4 you've heard today describing the pimavanserin
5 clinical trial program.

6 Firstly, to help understand the mean level
7 of benefit, I would like to describe the
8 improvement for a typical person with Parkinson's
9 disease psychosis receiving pimavanserin in the
10 020 study. At baseline, this person had severe
11 daily visual hallucinations, additional
12 hallucinations in the olfactory and auditory
13 domains, and delusions of mild severity.

14 The most severe symptom, visual
15 hallucinations, improved from daily to weekly.
16 This was a 2-point advantage on the SAPS-PD. There
17 was a resolution of delusions, a further 2-point
18 gain, and 1-point improvement in auditory and
19 somatic hallucinations.

20 This absolute improvement of 6 points
21 reflects the typical level of benefit across
22 participants receiving pimavanserin. This most

1 commonly involved a reduction in the primary
2 psychotic symptom, usually visual hallucinations,
3 from daily to weekly, with additional benefits on
4 other symptoms such as persecutory delusions.

5 For patients and their caregivers, the
6 difference between daily and weekly symptoms,
7 representing a 2-point improvement on the SAPS-PD,
8 is immense. When these symptoms are present daily,
9 they often last for 3 or 4 hours, and they're
10 totally preoccupying. The most common content of
11 clinically significant visual hallucinations is
12 intruders in the house. This is distressing for
13 the patient and for the caregiver.

14 An example would be a patient of mine who
15 sat by the kitchen window all day waiting for
16 intruders to arrive. He was extremely anxious and
17 distressed and was convinced they were entering the
18 house and stealing possessions.

19 At this level of intensity, insight into the
20 symptoms is lost, and it is impossible for either
21 the person with Parkinson's disease or the
22 caregiver to get on with normal life. The impact

1 on quality of life for both individuals is
2 absolutely massive.

3 Once symptoms are reduced to once a week,
4 they can still be distressing, but insight is often
5 preserved. In addition, the caregiver knows the
6 symptoms will abate, and they will have respite.
7 For most of the week, the person with Parkinson's
8 disease and their caregiver are able to go about
9 their normal lives to a significant degree. Impact
10 on quality of life is dramatically improved.

11 Whilst not all participants benefited from
12 pimavanserin and treatment response varied between
13 individuals, it is also important to highlight that
14 14 percent of participants in the 020 study had
15 complete resolutions of symptoms from a baseline of
16 quite intensive psychotic symptomatology. An
17 example of a typical participant with complete
18 resolution is shown on the slide. And as we've
19 already heard from Dr. Stankovic, these treatment
20 benefits were maintained for at least a year in
21 many of these individuals.

22 Based on a thorough review of randomized

1 controlled trials and cohort studies, I've compiled
2 the current slide to illustrate the efficacy and
3 safety of atypical antipsychotics for the treatment
4 of people with Parkinson's disease psychosis. The
5 table is based on my interpretation of the
6 evidence.

7 From recent work of Dr. Weintraub and
8 colleagues, it's clear that most people with
9 Parkinson's disease who are prescribed an atypical
10 antipsychotic receive quetiapine, olanzapine, or
11 risperidone. Although infrequently used, clozapine
12 is included in the table because it is the only
13 antipsychotic with established efficacy in people
14 with Parkinson's disease psychosis. Other atypical
15 antipsychotics are either ineffective or too poorly
16 tolerated to even be evaluated in randomized
17 clinical trials.

18 There has rightly been considerable focus on
19 mortality risk. There is an established increase
20 in mortality for atypical antipsychotic drugs in
21 people with Parkinson's disease, and the numerical
22 increase in mortality with pimavanserin has also

1 been described, albeit with a small number of
2 events.

3 There has also been a significant focus on
4 the propensity of most atypical antipsychotics to
5 worsen Parkinsonism, an impact which is not seen
6 with pimavanserin. There are, however, a wide
7 range of dangerous adverse events seen with
8 atypical antipsychotics, examples of which are
9 shown on the slide. Importantly, there is no
10 reported increase of any of these events associated
11 with pimavanserin treatment.

12 I would just like to focus on several of
13 these adverse events as important examples.
14 Neuroleptic malignant syndrome is a severe
15 condition characterized by worsening Parkinsonism,
16 muscle rigidity, fever, deteriorating cognition,
17 rhabdomyolysis, and significant mortality. In
18 people with Parkinson's disease psychosis treated
19 with atypical antipsychotics, neuroleptic malignant
20 syndrome occurs in a staggering 25 percent.

21 Orthostatic hypotension, often leading to
22 falls and related fractures, is a common problem in

1 people treated with atypical antipsychotics. Blood
2 dyscrasias are of course a well-known problem with
3 clozapine.

4 If I may summarize, psychotic symptoms are
5 distressing and extremely impactful in people with
6 Parkinson's disease. Not treating these symptoms
7 is just not an acceptable option, but we have a
8 problem. The majority of antipsychotics currently
9 used for the treatment of psychosis in people with
10 Parkinson's disease have no established efficacy
11 and all have concerning safety profiles.

12 Pimavanserin would be a very welcome
13 treatment option and address a critical unmet need
14 for people with Parkinson's disease psychosis.

15 Thank you.

16 MS. BHATT: Before we go on to clarifying
17 questions, we have a few people who joined the
18 panel. If you could please introduce yourself and
19 your organization.

20 DR. SARKAR: My name is Urmimala Sarkar.
21 I'm on the faculty of the University of California
22 San Francisco in the school of medicine, department

1 of medicine.

2 DR. FARCHIONE: Tiffany Farchione, deputy
3 director of psychiatry.

4 **Clarifying Questions to Applicant**

5 DR. BRENT: Are there any clarifying
6 questions for the applicant? Please remember to
7 state your name for the record before you speak,
8 and if you can, please direct questions to a
9 specific presenter.

10 Dr. Fahn?

11 DR. FAHN: Yes, Stan Fahn, Columbia
12 University. I have some questions about the
13 assessments, and it's basically I need to be
14 clarified about certain things on the primary
15 assessments and the secondary assessments.

16 I understand on the primary assessments that
17 from what you spoke, there are two observers
18 looking at the patient and asking questions through
19 a video session. And how does that work? I mean,
20 is the patient brought into a conference room where
21 there's a video set up, and is it the same two
22 observers for all 200 patients or is there

1 different observers looking and asking the
2 questions?

3 If somebody can please explain that to me.

4 DR. OWEN: Certainly. My name is Randy
5 Owen. I'm the senior vice president for clinical
6 development and chief medical officer for Acadia.

7 On this question of the methodology of the
8 central raters, Dr. Stankovic.

9 DR. STANKOVIC: We have employed the
10 separate research organization that professionally
11 does rating across psychiatric trials by the name
12 Medavante. And the central ratings were done by 17
13 trained psychometricians at a central site in New
14 Jersey.

15 Those raters, just for a second to digress,
16 those raters were blinded, as I mentioned earlier,
17 for all of the study procedures, and they performed
18 regular inter-rater reliability exercises and
19 confirmed the high level of inter-rater variability
20 at .93.

21 The process at the site was that a caregiver
22 completed a short questionnaire that was

1 transmitted to the rater on the status of the
2 patients, and then patient and caregivers were
3 taken into a separate video conferencing room at a
4 site. One site member was there to facilitate
5 connecting with the rater, and caregiver and the
6 patient were in the room during the interview.

7 If there were any questions for the
8 caregiver, that was also available to the rater,
9 but nothing other than that.

10 DR. FAHN: So would the single patient,
11 single subject, examined at baseline 2 weeks,
12 4 weeks, 6 weeks -- are the same two raters each
13 time for that person, or are there different raters
14 evaluating that patient?

15 DR. STANKOVIC: As a central rater, there
16 were certain rules in rating, one being that same
17 rater was not performing assessment at baseline and
18 at the end of the study. During study visit, it
19 was recommended that there is no same rater making
20 ratings, central ratings, but it was occasionally
21 allowed. But beginning at the end of the study,
22 that was not the case.

1 At the site, the treating clinician was
2 rating the patient on the Clinical Global
3 Impressions scale.

4 DR. FAHN: And for the assessments at the
5 site, are the investigators neurologists, movement
6 disorder neurologists, psychiatrists, who does the
7 UPDRS exams at the sites?

8 DR. STANKOVIC: Right. I will ask
9 Dr. Isaacson, who was the investigator on the site,
10 to maybe comment on the procedures at the site.

11 DR. ISAACSON: Thank you, Dr. Fahn.

12 So this is actually what we do in the
13 clinic. So patients would come in for a study
14 visit, and they would be taken first to the video
15 room. It's an exam room with a T1 line and a video
16 camera. And they and the caregiver would be the
17 only ones speaking with the remote interviewer,
18 which was different at every visit.

19 Then they would go and do the other
20 assessments for the visit, and either myself at my
21 site or one of the trained -- who are trained on
22 UPDRS and met the certification process, that was

1 typical, would perform parts II and III each time
2 and a CGI, being blinded to what occurred behind
3 the closed video door.

4 So there were actually distinct ways of
5 assessing the improvement that was seen, either
6 with SAPS-PD for the blinded rater or the CGI
7 performed by a primary investigator at each site.

8 DR. FAHN: So in other words, each site was
9 a movement disorder neurologist, basically, and
10 somebody trained in UPDRS?

11 DR. ISAACSON: So some sites would be a site
12 that was not a movement site, would be a psychiatry
13 site or other site, where the person performing the
14 CGI or UPDRS would have received the adequate
15 training at the investigator meeting and met those
16 credentialing qualifications.

17 DR. BRENT: Dr. Ionescu.

18 DR. IONESCU: Hi. I just have a brief
19 safety question. As you know, many patients with
20 Parkinson's disease also have comorbid mood
21 disorders and are put on serotonergic modulating
22 agents for their depression.

1 Just curious to know from a safety
2 perspective if any of these patients were on
3 antidepressants with serotonergic properties and
4 how the safety with this medication turned out.

5 DR. OWEN: The question of antidepressants
6 and safety, Dr. Demos.

7 DR. DEMOS: There were subjects taking
8 serotonergic reuptake inhibitors.

9 Slide up. As we see here, this is in the
10 middle, subjects with drug and without drug. There
11 were 40 subjects randomized to pimavanserin that
12 had treatment for depression with a
13 particular -- and though it appears that they may
14 have had more adverse events, it's a slightly
15 different population now that they're being treated
16 for depression. So we're not sure that you can
17 really make any assessment of it. But overall,
18 adverse events were reported at a slightly higher
19 rate.

20 Notice that the placebo group also reported
21 adverse events at a slightly higher rate of almost
22 70 percent versus just under 60 percent in the

1 placebo group without serotonin reuptake
2 inhibitors.

3 DR. BRENT: Dr. Grieger?

4 DR. GRIEGER: Tom Grieger. One simple
5 question, in the Cummings Lancet study that was
6 published in 2013, it appears to be the same study,
7 what they refer to are a 40-milligram dose. Is
8 that just a matter of bioavailability of a salt
9 versus the active compound or --

10 DR. OWEN: That is correct. It's the
11 difference between the salt versus the active
12 compound.

13 DR. GRIEGER: Okay. And the second
14 question, I don't know if you have a graphic for
15 this or not, but a distribution at baseline and at
16 the endpoint for each of the symptom categories of
17 the SAPS-PD, rather than just a global score, what
18 symptoms seemed to be most responsive across that
19 instrument?

20 DR. OWEN: Dr. Stankovic.

21 DR. STANKOVIC: Yes, we do have that. Slide
22 up, please. The most responsive symptoms were

1 visual hallucinations and a global hallucination
2 assessment followed by the global delusion item on
3 the 9-item scale.

4 DR. GRIEGER: Thank you. That answers it.

5 DR. BRENT: Dr. Winterstein?

6 DR. WINTERSTEIN: Thank you. I have a
7 follow-up question on this. I tried to understand
8 the newly generated subscale, the SAPS-PD scale, in
9 relationship to the originally developed scale that
10 was developed, I think, two decades ago or one
11 decade ago. I mean, typically, there would be a
12 new psychometric testing of some kind that would
13 look at how relevant the subscale, the selection of
14 those items is to the patient population that's
15 being tested.

16 Could you contrast the original SAPS scale
17 with the selection of those 9 items, number one; so
18 essentially, what was left out? And then perhaps
19 explain to the committee those items that were left
20 out, are they relevant to Parkinson's patients, or
21 are they not?

22 So basically, what we have left is really

1 the general universal symptomatology that we would
2 see in psychosis in Parkinson's patients, and then
3 what kind of validity and reliability testing was
4 done with this new subscale. And then building on
5 this, is there any reference to a clinically
6 significant difference in the original SAPS scale
7 that has been validated?

8 My final question that relates to this is,
9 you referred in your presentation to patients who
10 had moderate to severe symptoms of psychosis, but
11 when I'm calculating this SAPS-PD subscale, from
12 what I understand is the ranges, the anchors are
13 zero to 45. Yet, the average of patients who were
14 enrolled, their score was 15.

15 So how would that explain a symptomatology
16 of moderate to severe? To me, that sounds mild if
17 I assume that that scale is actually linear.

18 DR. OWEN: So I heard, I think, five
19 questions. One was comparing the SAPS-PD to the
20 SAPS H and D. I didn't quite get your second
21 question, but the third question was discuss
22 validity and reliability, the clinical significance

1 of it, and then how to explain the moderate
2 severity. But could you repeat your second
3 question, please?

4 DR. WINTERSTEIN: Yes. Second was, so if
5 you look at the symptomatology of psychosis in
6 Parkinson's patients, since you produced the
7 subscale, how much does the subscale cover that
8 symptomatology and what was left out? And then the
9 clinical significant difference referred to the
10 original SAPS scale, not to your subscale. I think
11 your presentation there was quite comprehensive,
12 but I would like to see or to know if there any
13 clinical significant, meaningful report that had a
14 value that has been reported for the original
15 scale.

16 DR. OWEN: So for the second question, how
17 does the SAPS scale capture the psychotic symptoms
18 of Parkinson's disease?

19 DR. WINTERSTEIN: Yes, and relative to the
20 original scale, what's left out.

21 DR. OWEN: Relative to the original.

22 Dr. Stankovic.

1 DR. STANKOVIC: The selection of 9 items for
2 SAPS-PD from the 20 items is based on four prior
3 studies. One is a clozapine study and three prior
4 pimavanserin studies. The frequency of items at
5 baseline was looked at, and the items with a higher
6 frequency were selected as informative for the
7 Parkinson's disease psychosis.

8 Slide up, please. As you can see, these are
9 all four studies, and the baseline status and
10 frequency of reported items at baseline for each
11 particular study. Based on this review, 9 items
12 were selected.

13 Next slide, please, up. This is the direct
14 comparison of the items that are checked in blue,
15 are 9 items selected for the SAPS-PD scale. You
16 will notice that in both on hallucinations and
17 delusion, there is one global item that is retained
18 to capture other symptoms that are not captured on
19 the individual items in either hallucination or
20 delusions module.

21 The validation of the scale was reported in
22 the Voss, et al. article in 2012, where the scale

1 is correlated to the CGI clinician assessment.

2 Slide up, please. This is that correlation
3 of the change in SAPS-PD vis-à-vis each of the
4 items on the CGI Improvements scale. And that work
5 has reported that the ability of the scale to
6 detect change and reliability of the scale is
7 retained.

8 We performed, based on the study 020,
9 similar correlation, which I will present right
10 now.

11 Slide up. This is the same comparison from
12 the study 020. Orange represents the delusion, and
13 blue, hallucination subscore. But the totality of
14 the box is the items.

15 So they look very comparable to the -- and
16 finally, in respect to the -- we did analysis on
17 the full SAPS H plus D 20-item scale, and that
18 analysis essentially confirmed. And it's very
19 similar to the analysis of the SAPS-PD scale.

20 So we conclude, on the basis of that, that
21 we captured in the study all relevant items on
22 psychotic items.

1 DR. BRENT: Dr. Pickar?

2 DR. PICKAR: Thank you.

3 I have a few questions. I didn't see
4 anywhere, I was a little surprised, the data with
5 reference to concomitant medications that you're
6 giving them. Psychosis and hallucinations
7 certainly exist in Parkinson's as in advanced
8 without medication, but the effect of dopamine
9 agonist, whether it's Sinemet or direct dopamine
10 agonist, for that matter and the MAO inhibitors,
11 causing delusions and mania has been the hallmark
12 of this for a lot of years; not that it doesn't
13 exist without it, but by far more common.

14 I was surprised that the data didn't show
15 what in dosages, what medications the patients were
16 treated, and what the analysis was like by
17 medication. You're making a very clear statement
18 this is a broad antipsychotic. I do not know, and
19 I'm curious how this interacts with medications
20 they're being given.

21 Number two, you had a large number, 190
22 patients, who treated with this drug for

1 schizophrenia, which is the hallmark of psychosis.
2 No comment whatsoever about how hallucinations or
3 delusions or whatever were affected in that
4 population, and yet you're talking very broadly of
5 this as an antipsychotic. You must have made the
6 comparison to other antipsychotics multiple,
7 multiple times in the same frame of reference.

8 Third, do you have films of any of those
9 centralized ratings? It's very common when you do
10 them to have films and to spot audit them the way
11 somebody would look at handwritten rating forms.
12 You have a very small effect here. It's consistent
13 and statistically significant, but it's small. And
14 I sure think taking a look at how those ratings
15 were gotten, what those patients looked like, would
16 be a very valuable thing for the agency.

17 DR. OWEN: So I've heard three questions,
18 and one is what does the data look like, the
19 efficacy data by the concomitant medications for
20 Parkinson's disease? What did we see within the
21 schizophrenia trial, as well as do we have films of
22 the central ratings?

1 DR. PICKAR: Along those lines, were any
2 patients drug free? Did you treat -- have you used
3 this drug on any Parkinson's patient that wasn't
4 treated with dopamine agonist of some sort?

5 DR. OWEN: The vast majority of the patients
6 were treated with a Parkinson's disease medication,
7 Sinemet, for example.

8 DR. PICKAR: Were there some drug free that
9 you could pull out for us?

10 DR. OWEN: So we will have to get back to
11 you for that, I think --

12 DR. PICKAR: And do you have the data
13 analyzed by --

14 DR. OWEN: -- we will get back --

15 DR. PICKAR: -- treatment and dose -- do you
16 have data analyzed by concomitant treatment?

17 DR. OWEN: One moment. I'd like to have
18 Dr. Stankovic comment, please.

19 DR. STANKOVIC: As presented, all patients
20 received Parkinson treatment in the study --

21 DR. PICKAR: There was no data presented as
22 to what Parkinson's medicines --

1 DR. STANKOVIC: Oh, okay.

2 DR. PICKAR: -- the ranges of that, and you
3 globally said that -- this gentleman here just said
4 some of the patients were drug free.

5 DR. STANKOVIC: Right, right.

6 DR. PICKAR: I think it's extremely
7 important, particularly how you're trying to
8 position this, and you've been saying it over and
9 over and over again as a new non-dopaminergic
10 antipsychotic.

11 DR. STANKOVIC: Yes, we do have -- slide up,
12 please. This is the proportion of patients that
13 received different classes of anti-Parkinson drugs
14 in the trial both for 34-milligram and placebo.
15 And we did --

16 DR. PICKAR: So it would appear that -- I'm
17 not sure I'm getting right -- 90 plus percent,
18 94 percent were on Sinemet; is that correct?

19 DR. STANKOVIC: Yes.

20 DR. PICKAR: And some amantadine on top of
21 it, and other dopamine agonists as well, must be on
22 top of Sinemet because 42 percent of the patients

1 had it. And some MAO inhibitors.

2 How did the data -- how did the responses
3 differ based on medication treatment?

4 DR. STANKOVIC: We did analysis through some
5 classes of drugs where this was -- we had enough
6 patients to do that.

7 Slide up, please. This is the primary
8 outcome, and then goes -- some anti-dementia and
9 anticholinesterase inhibitors, so that and SSRIs.
10 But we do not have analysis on the different
11 classes of anti-Parkinson's drugs.

12 DR. PICKAR: What is no -- well, we could go
13 on, on this, but I'm still unclear with
14 relationship, because in looking at this, you can
15 see ranges of responses here that are quite
16 different. No prior adjustment, I don't know what
17 that means, and that's not much. Some of the other
18 ones were --

19 Okay. It doesn't particularly clarify. It
20 raises questions in my mind. I don't think that's
21 teased apart well.

22 Second question was schizophrenia data,

1 because you're referring to this as you did, sir,
2 multiple times as an antipsychotic, so forth and so
3 on. How does it work in the fundamental psychosis
4 that we deal with every day, the most important
5 one?

6 DR. STANKOVIC: I'm sorry. Let me just
7 clarify the question.

8 DR. PICKAR: What's its effect in
9 schizophrenia? It's relevant because next to this,
10 the largest number of patients exposed to this drug
11 had schizophrenia, and that is the fundamental,
12 most important psychosis in a broader sense. And
13 you are referring to this broadly as an
14 antipsychotic.

15 What is its efficacy in schizophrenia?

16 DR. STANKOVIC: We have focused evaluation
17 on the Parkinson's disease psychosis. There were
18 two studies done some years ago in schizophrenia,
19 but the larger study reported is a study that
20 essentially evaluated low dose of risperidone and
21 haloperidol together with pimavanserin adjunctively
22 versus the higher dose.

1 In that study, the low-dose risperidone plus
2 pimavanserin performed approximately the same as
3 the 6-milligram risperidone, which was not the case
4 with haloperidol. But as I said, following those
5 studies, we pursued a different direction in
6 developing and evaluating drug in Parkinson's
7 disease psychosis.

8 DR. PICKAR: Did you see its effectiveness
9 in that population on hallucinations?

10 DR. STANKOVIC: Yes, there was a similar
11 effect as the 6-milligram dose risperidone on both
12 positive and negative symptoms, as a matter of
13 fact.

14 DR. PICKAR: Okay. We can go into that in
15 more detail. I'm not completely clear on that as
16 well. And are there films of the ratings that can
17 be audited?

18 DR. STANKOVIC: We do not have those.

19 DR. PICKAR: There are no films? You did
20 this live on Skype or what did you --

21 DR. STANKOVIC: Yes, it was a live video
22 feed.

1 DR. PICKAR: And no records of that, no
2 pictures, no filming of that? You had 17 raters,
3 did I hear this, doing this by -- I'll just say, if
4 I was in the agency, I'd like to see some --

5 DR. STANKOVIC: I will have to confer with
6 our contract organization whether they have records
7 on that --

8 DR. PICKAR: Fair enough.

9 DR. STANKOVIC: -- but we do not have those.

10 DR. PICKAR: And people drop out of the
11 study, 2 percent for hallucinations and 1.5 percent
12 for psychotic symptoms. These were people who were
13 treated with the 2A inverse agonists, had to quit.

14 What happened? Did they become more
15 hallucinatory, or did hallucinations -- I don't
16 know why -- were they -- why were they considered
17 AEs that made them stop the study when 2 percent
18 hallucinations, 1.5 percent were psychiatric
19 problems?

20 DR. OWEN: On the question of worsening
21 hallucinations, other psychiatric symptoms, we
22 looked thoroughly into that and concluded that it

1 did not cause -- or pimavanserin was not associated
2 with worsening psychotic symptoms.

3 But let me have a moment to explain how we
4 came to that conclusion. It begins with the
5 description of different physicians can look at a
6 symptom complex and code it differently. One
7 person might code it as a hallucination. Somebody
8 might code it as a visual hallucination. Somebody
9 else might code it as a psychotic symptom.

10 So to begin with understanding this
11 question, we had to look at the totality of
12 psychiatric symptoms.

13 Slide up, please. These are the psychiatric
14 symptoms that were observed in the study. As you
15 can see on the very top row, 33 patients had an
16 adverse event of psychiatric symptoms on
17 pimavanserin, 32 on placebo.

18 We grouped the different psychotic symptoms
19 together. So as you can see, there's a psychotic
20 disorder, hallucination, hallucination visual,
21 somatic hallucination. Down at the bottom, a
22 psychiatric symptom that was coded by the

1 physician, which was clearly hallucinations in the
2 narrative.

3 Slide up, please. When we combined and
4 grouped these different terms together to see the
5 totality of increased psychotic symptoms, this is
6 what we find. Seventeen of patients on
7 pimavanserin, 17 patients on placebo.

8 Here you can see some of the different terms
9 that were used. On some of the terms, pimavanserin
10 was higher than placebo. On other terms such as
11 psychotic disorder, pimavanserin was less than
12 placebo. In totality, though, it was comparable.

13 DR. BRENT: Dr. Narendran?

14 DR. NARENDRAN: I have a very simple,
15 straightforward question. Slide CE-27, you
16 contrasted the effect size for pimavanserin with
17 the antipsychotic drugs, but in the raw magnitude
18 delta change for the SAPS-PD as well as the SAPS H
19 plus D is about 3 points.

20 Do you have this same slide showing the raw
21 change in schizophrenia contrasted to that 3-point
22 change?

1 So in other words, if you deconvolve the
2 standard deviation and just show the raw change
3 delta, like is the schizophrenia trial about the
4 same, or is it A plus or minus 16 to get to that
5 point? I'd like to look at that slide if you have
6 it.

7 DR. STANKOVIC: We do not have a slide, but
8 I would like to try to respond to your question.

9 All of these effect sizes for
10 antipsychotics, actually, most of them, are done on
11 the basis of the movement on PANSS scale, Positive
12 and Negative Scale for Schizophrenia. That scale,
13 to remind everybody, is 30 items, 7 ratings, 210,
14 zero to 210 span.

15 What we usually see in schizophrenia trials
16 in a good schizophrenia trial is about 20 points
17 change on the active drug and about 10-point change
18 on placebo for a total of 10 points change. So
19 we're talking about 10-point change over the scale
20 of 210 possible items. And just to add for the
21 previous question, usually when entered into the
22 trial, schizophrenia patients have a score about 75

1 to 80 on the average, which is way below the -- and
2 we also considered them to be moderately severe in
3 that.

4 Now, to put all of that in context, the
5 change we saw on the SAPS-PD, SAPS-PD is 9 items on
6 a 5-point ratings, which is 45 items. We see a
7 6-point difference for the pimavanserin patients
8 versus 3-point difference on the placebo for a
9 3-point change.

10 So we believe that is quite comparable, as
11 much as one can think about that. It is very hard
12 to put that in any data context as we don't have
13 direct data.

14 DR. BRENT: Hi. Ms. Witczak?

15 MS. WITCZAK: Hi. Thank you.

16 I guess David's asked a couple of my
17 questions, but one of them is in the -- a little
18 bit more clarification on when we got to the
19 9 alternate questions, the scale. Were patients
20 included in that? I mean, who ultimately decided
21 what the 9 were going to be? And if patients
22 were -- I mean, how much were they weighted into

1 that decision? That's the first.

2 Then the other was really going back to some
3 of that schizophrenia data, and I'm guessing when
4 you call it off-target liabilities, it's really off
5 label. And I know that ultimately it's not about
6 you promoting it. But how do you ensure
7 that -- and this is more assuming it got
8 approved -- that it would stay in marketed just for
9 the psychosis of Parkinson's disease? Because
10 that's a big potential area of business.

11 DR. OWEN: And I'm sorry. I missed the very
12 tail end of your third question. How do we ensure?

13 MS. WITCZAK: Oh, how do you ensure -- I
14 mean, what are your plans that you would just
15 ensure that it would be directly targeted to the
16 physicians and clinicians that are treating
17 psychosis in Parkinson's disease when there's a
18 huge potential for off-target or off-label use?

19 DR. OWEN: And just a clarification on your
20 second question about schizophrenia, could you
21 repeat that question, also?

22 MS. WITCZAK: Yes. I mean, I think that's

1 basically it. I mean, you would --

2 DR. OWEN: It's the same question?

3 MS. WITCZAK: Right, it's the same. So it's
4 really two questions.

5 DR. OWEN: So then, what I've heard are two
6 questions. One is a little bit more on the
7 development of the SAPS-PD, how did we select the 9
8 items specifically. But then the other question is
9 how do we ensure that it's Parkinson's patients and
10 not other patients as well.

11 Dr. Stankovic.

12 DR. STANKOVIC: The selection of items,
13 9 items from the SAPS H and D scale, is based on
14 the frequency of reports. These items are based on
15 the SAPS interviews done with the input of patient
16 and the caregiver in the course of the interview.
17 So that was the input into reporting certain items
18 and then simply frequency or the most frequent
19 items were chosen as a representative of psychotic
20 symptoms in Parkinson's disease psychosis.

21 In regard to labeling, obviously, we are
22 looking forward to discuss with the agency the

1 labeling, so any comments will be premature.
2 Particularly, we are not in a position to make such
3 conclusion at this point. But the application is
4 for treatment of psychosis associated with
5 Parkinson's disease, and we fully understand and
6 expect that that will be reflected in the label.

7 DR. GORDON: Mark Gordon, industry
8 representative. Did any of the subjects undergo a
9 change in their Parkinson's medications either just
10 prior to the randomization or during the conduct of
11 the study on treatment?

12 DR. OWEN: Dr. Stankovic.

13 DR. STANKOVIC: The product goal specified
14 that patients are on a stable Parkinson's
15 medication, so the change in medications were not
16 allowed.

17 DR. GORDON: And were there any protocol
18 violations of this type?

19 DR. STANKOVIC: I don't have that on the top
20 of my head. I will have to check and get back to
21 you on that.

22 DR. BRENT: Dr. Gerhard?

1 DR. GERHARD: This is a question, I believe,
2 for Dr. Demos, but maybe some of the other
3 speakers.

4 The one point that was consistently stressed
5 regarding the severe adverse events and
6 particularly the mortality findings were that there
7 was no unifying pathophysiologic process.

8 So one question, isn't that exactly what we
9 observed for the second-generation antipsychotics
10 or both in the trial data and meta-analyses from
11 trial as well as observational work, that there
12 aren't specific causes of death that seem to be
13 driving the mortality, so we have a very comparable
14 situation?

15 Then the second, the way I at least heard
16 that statement was in a sense to be a reassuring
17 statement, that we don't have a unifying process in
18 a sense that might not be real. So I think that's
19 an argument that would have a lot of weight if we
20 were looking at observational data. So where this
21 might -- the absence of the unifying process or a
22 specific cause of death that was driving this was

1 driven by potential uncontrolled confounding or
2 other biases.

3 But here we see the findings from clinical
4 trial data. So the lack of an observed unifying
5 pathophysiological process, I don't think can be
6 used as a reassuring observation here, both for the
7 antipsychotics in general in the elderly with
8 dementia or for the particular product under
9 discussion today.

10 DR. OWEN: And so the question that I'm
11 hearing is a little bit more on the SAEs
12 themselves, the lack of unifying mechanism is
13 itself not simply the -- it's more than just a lack
14 of a unifying pathophysiology, and you're asking
15 our comment on that.

16 DR. GERHARD: And particularly in comparison
17 with what we know about the second-generation
18 antipsychotics and the well-known black box warning
19 on increased mortality risk in the elderly with
20 dementia.

21 DR. OWEN: So I'd like to address in a
22 couple of different ways, but first of all, we

1 acknowledge that there's an imbalance in SAEs and
2 deaths. We completely recognize that fact, and we
3 acknowledge that disparity.

4 Having said that, we have done a lot of work
5 to thoroughly evaluate this, and I'd like to share
6 just a couple of more salient features, one of
7 which is we investigated it ourselves, of course,
8 but we also brought in additional experts, one a
9 cardiovascular expert, one an expert who has many
10 years of clinical trial expertise in drug safety,
11 to help us do signal identification evaluation.

12 Certainly, we've looked at the literature.
13 We've looked at the antipsychotic safety profiles,
14 including their deaths and such, as well as their
15 other adverse events.

16 Altogether, you're right. We did not
17 identify a unifying theme, and these illnesses, the
18 SAEs themselves and the deaths, are consistent with
19 the patient's age, their illness, their
20 comorbidities. But within the SAEs themselves, we
21 think that there are other important categories of
22 safety to be also considered.

1 So, for example, within the SAEs, certainly
2 four or five of them, the patient completed. There
3 was a breast cancer that was identified
4 pre-randomization. There was a bronchitis that was
5 25 days off drug.

6 When you look at overall, though, the
7 imbalance of SAEs, you would think that it might
8 show up in other ways as well. When we looked at
9 overall adverse events, it was similar between drug
10 and placebo. When we looked at laboratory
11 abnormalities, laboratory AEs, when we looked at
12 our toxicology profiles, these were generally
13 comparable to placebo. The toxicology identified
14 no safety risk.

15 So we think that potentially looking at only
16 the SAEs deaths may potentially overestimate the
17 risk. Nonetheless, it is there, and we do
18 acknowledge it.

19 DR. BRENT: We have four more questions
20 before we go on break, and now Dr. Elmore.

21 MS. ELMORE: I realize that it was not
22 presented today, but given the animal data, was

1 there any specific monitoring of patients in the
2 various clinical trials for renal for pulmonary
3 disease?

4 DR. OWEN: So the question was specific
5 pulmonary findings in the clinical data?

6 MS. ELMORE: Or renal.

7 DR. OWEN: So yes, we did specifically look
8 at that in multiple contexts. There were no renal
9 events specifically in the double-blind trial.
10 There were a few respiratory events, two patients
11 with dyspnea and respiratory on pimavanserin, I
12 believe. And in general, it was comparable to
13 placebo.

14 So we saw nothing to suggest organ toxicity
15 in the double-blind trials.

16 MS. ELMORE: So that's what was reported,
17 but it was monitored for, correct?

18 DR. OWEN: It was monitored in the sense
19 that we were aggressively looking for adverse
20 events. That is correct.

21 MS. ELMORE: Okay. So would it be fair to
22 say, then, that if it did exist, it would be so

1 minimal as to be clinically insignificant?

2 DR. OWEN: I'm sorry. I didn't quite hear
3 what you said.

4 MS. ELMORE: So if it did exist, would it be
5 fair to say that it was so minimal as to be
6 clinically insignificant?

7 DR. OWEN: We would agree with that. I
8 mean, because the definition of the adverse events
9 is clinically meaningful worsening of a condition.

10 DR. BRENT: Dr. Schmid?

11 DR. SCHMID: I just had a couple questions.
12 So I'm comparing slide CE-11 and CS-9, and I'm
13 trying to get a little bit better handle on the
14 difference between study 020 and study 12. So 11
15 is the flow chart for study 020, and it shows a
16 little bit of an imbalance in the randomization
17 numbers. There's a few more in the treatment and
18 in the control, and it also shows that there's
19 quite a discrepancy in the AEs and the
20 discontinuation rate. They're 10 on treatment and
21 two on control.

22 In slide CS-9, which combines studies 012

1 and 020, there is an even larger difference in the
2 randomization numbers but now in the opposite
3 direction. And the AEs are now a little bit closer
4 together, I guess, because there was not as much of
5 a difference in discontinuation.

6 So I'm just wondering, I'm just sort of
7 trying to understand the differences between the
8 two studies and whether these are meaningful
9 differences or whether you think they're just by
10 chance.

11 DR. OWEN: I actually heard two questions
12 there. One is the disparity in the randomization
13 numbers from a statistical point of view. The
14 other was the disparity or lack of it within the
15 AEs themselves, the discontinuations.

16 Dr. Stankovic.

17 DR. STANKOVIC: The most significant
18 difference between study 012 and study 020 is that
19 study 020 is done exclusively in North America and
20 predominantly in the United States with a couple of
21 sites in Canada. The study 012 is done in three
22 regions.

1 So looking at discontinuation and adverse
2 events, there is always the element of the regional
3 impact on the frequency of adverse events,
4 frequency of discontinuations between the regions,
5 which we see in most of the trials we do globally.

6 So I think that some of the differences you
7 may see where the data is pooled as opposed to
8 individually comes from those regional differences.

9 DR. OWEN: And then you had a question also
10 about the adverse events, discontinuations, and
11 such.

12 DR. SCHMID: So one was the
13 discontinuations, and the other was just the
14 differences in the randomized numbers, which I
15 thought it was a one-to-one randomization. So I
16 was just a little surprised that they were so
17 different.

18 DR. OWEN: So it was a one-to-one
19 randomization, but Dr. Knowles, would you care to
20 comment?

21 MR. KNOWLES: My name is Mark Knowles. I'm
22 head of biostatistics at Acadia.

1 First, I'd like to address your first
2 question on CE-11 and the imbalance in the two arms
3 and the randomization for study 020. The
4 randomization scheme used permuted blocks within
5 study site, and there was a total of 54 sites that
6 randomized patients. And so that imbalance was
7 simply a result of incomplete blocks within study
8 sites.

9 Then your question on CS-9 and why the ends
10 were so different there, CS-9 included all three
11 6-week placebo-controlled studies. So the placebo
12 group includes the placebo group from the 014
13 study, which did not include the 34-milligram dose.

14 DR. OWEN: And on your second question
15 regarding the discontinuation rates, we agree with
16 you. Certainly, on study 020, there were more
17 discontinuations on pimavanserin than placebo.
18 Some of those have been discussed already this
19 morning with regard to the SAEs, and some of those
20 were the SAEs that occurred early.

21 As we get more data and we feel that the
22 data becomes more stable, we are finding that the

1 discontinuations are becoming more comparable.

2 DR. BRENT: David Brent. I have three
3 questions. The first is there was a comparison of
4 the efficacy for this condition using
5 antipsychotics, but most of the studies use the
6 BPRS. And my understanding was that you developed
7 a measure that would be more sensitive to detecting
8 changes in this condition. So the only study that
9 did use that measure was the clozapine study where
10 there was a positive effect.

11 So I guess I'd like you to comment on
12 whether the failure to find an effect in those
13 could have been because of a difference in the
14 rating scale.

15 The second is whether there were differences
16 in the criteria to come into the study because in
17 020, you had a psychosocial run-in, and it seemed
18 like you took mostly moderate to severe patients.
19 In the one study where there were mild to moderate,
20 there wasn't an effect.

21 So I'm just wondering in terms of
22 comparability of those studies to this 020, if you

1 could comment on that. And perhaps there still is
2 an open question about whether these other drugs
3 could be effective. That's the first question.

4 The second is in terms of the outcome on the
5 SAPS-PD, do you have data to compare the proportion
6 in the drug versus placebo that it showed a
7 50 percent or greater improvement?

8 Then, the rationale for presenting a
9 modified intent to treat rather than including all
10 the subjects, especially because some of the
11 ones -- I think as Dr. Schmid was alluding to, some
12 of the ones who were removed were removed for the
13 condition that they were being treated for.

14 DR. OWEN: So I heard three questions.
15 Actually, I had four written down. One was on the
16 modified ITT. One was on looking at response by
17 the 50 percent cut, and another one was on the
18 slide of comparisons of antipsychotics, could it be
19 differences of scales and such like that.

20 I'd like to take the last one first and just
21 remind everyone that we had a sensitivity analysis
22 of all randomized patients, true ITT analyses, that

1 also showed that pimavanserin was statistically
2 superior to placebo.

3 But on the other two questions, I'd like to
4 address to Dr. Stankovic regarding the comparisons
5 as well as placebo responders, 50 percent.

6 DR. STANKOVIC: You are absolutely right,
7 BPRS is a much broader instrument than the SAPS-PD.
8 It is possible that the hypothesis you put forward
9 had some reasonable possibility that that could
10 have been the case.

11 Why we believe that probably is not is that
12 those trials, actually placebo performed better
13 than the drug. So even if you take into account
14 the instrument, and the instrument may not be the
15 most sensitive instrument, one would not expect
16 that olanzapine does worse than placebo as well as
17 Seroquel does worse than placebo.

18 DR. BRENT: And what about the entry
19 criteria, whether they --

20 DR. STANKOVIC: Yes. We believe that there
21 were comparable patients. I cannot exactly be
22 precise about that because clinical trials differ,

1 and these are very small trials, so that there
2 could have been some differences in that respect.
3 But in overall, we would think that it is a similar
4 patient population included.

5 In respect to the question of the primary
6 analysis being done on the modified intent-to-treat
7 population and not in all randomized patients, we
8 did actually do all analyses on all randomized
9 patients under conservative assumptions that those
10 patients that dropped out were non-responders, for
11 instance.

12 Let me just ask for that slide. Can I get
13 all randomized CGI response for --

14 DR. BRENT: I saw the analyses. I was just
15 asking the rationale for making your primary
16 analyses on the modified --

17 DR. STANKOVIC: The rationale is that we did
18 not have the post-baseline assessment on the
19 primary outcome measures, so we could not include
20 that. But as I said on the CGI, we did analysis on
21 all randomized patients assuming that those that
22 drop out were non-responders and essentially got

1 the same results.

2 DR. TEMPLE: Didn't you also ask what the
3 50 percent response rate was?

4 DR. BRENT: Yes.

5 DR. TEMPLE: You didn't answer that.

6 DR. STANKOVIC: I'm sorry.

7 DR. BRENT: I just wanted to know what the
8 difference between the groups --

9 DR. STANKOVIC: Slide up. I'm sorry.

10 So these are the differences at every
11 percent reduction from baseline. In psychosis
12 trials, different cutoffs are used for reduction
13 from baseline. I mean, 50 percent is fairly high
14 threshold for a psychosis trial.

15 Usually in schizophrenia trials, for
16 instance, more frequently one sees 30 percent
17 reduction, even sometimes 20 percent reduction
18 from -- but these are -- we essentially produced
19 all of the data.

20 DR. BRENT: Thank you.

21 DR. STANKOVIC: In terms of -- if I may just
22 add one thing. One thing that we also observed, as

1 you go through these cutoffs, we see a more robust
2 response essentially at the more severe -- a larger
3 difference than -- this may be also some indication
4 of the variability of the psychotic symptoms in
5 these patients so that in the placebo group, there
6 is a lot of movement around mild change from
7 baseline.

8 That may be the reason why many of these
9 trials in Parkinson's disease psychosis patients
10 are essentially not successful.

11 DR. BRENT: Thank you.

12 Dr. Duda?

13 DR. DUDA: John Duda from Philadelphia. I
14 think this is for Dr. Isaacson, but maybe others.

15 So I think the current standard of care for
16 the management of PD psychosis includes withdrawing
17 medications, both PD and non-PD medications that
18 might be contributing to the delirium or psychosis,
19 including things like amantadine and dopamine
20 agonists.

21 How was this taken into account in the trial
22 design? There were a fair number of people on

1 amantadine, and I would never have started an
2 antipsychotic before taking somebody off of
3 amantadine or even a dopamine agonist.

4 DR. OWEN: I'll call Dr. Isaacson to come
5 forth, but I'd like to reiterate that the
6 Parkinson's medicines were required to be stable
7 during trial itself. But for further comment on
8 the difficulties of treating, Dr. Isaacson.

9 DR. DUDA: But the main point is not during
10 the trial but before considering adding an
11 antipsychotic, how was that decision made?

12 DR. ISAACSON: Yes, John. This is how -- as
13 you point out, this is how we treat Parkinson's
14 patients. The biggest problem we have in
15 Parkinson's disease psychosis is that we lower
16 those medicines we use to try to make people not
17 fall and continue on with their lives and mobility.
18 And presumably, these patients have tried all these
19 things. About 20 percent of the patients came in
20 on quetiapine and had to be washed off, for
21 example.

22 These are patients you try to take away some

1 of the medicines. We don't want them on amantadine
2 and dopamine agonists. These are medicines that we
3 think increase psychosis. You try to take them
4 away and a patient falls, so you put it back. You
5 lower this. They get slower. You raise that.
6 They have less tremor. They have more psychosis,
7 so we lower the medicine. It's a constant
8 balancing act we have because we don't have an
9 effective antipsychotic really that prevents us
10 from having to take away the dopamine medicines.

11 So the idea is that these patients were
12 having moderate to severe symptoms not because of a
13 scale number but because this impacted their daily
14 lives. It was troublesome to themselves or
15 caregivers. It was making them have more care that
16 they needed and interfering with their ability to
17 treat their Parkinson's mobility symptoms
18 optimally.

19 They're on these medicines. It probably
20 reflects a real-world experience of what these
21 patients go through trying to take less medicines
22 and having less mobility and trying to raise it and

1 having more psychosis.

2 DR. DUDA: So just to clarify, it was not
3 the intent that adding this medication be the
4 first-line management decision?

5 DR. ISAACSON: No. These were patients who
6 had Parkinson's on average for 10 years, so they
7 were into that range where motor fluctuations, not
8 only the psychosis and mobility, but they go three
9 hours, they're doing better; a couple of hours,
10 they're not doing so well, on and on throughout the
11 day, every day.

12 They had Parkinson's disease psychosis I
13 think on average for about three years when they
14 came into the trials. So during those three years,
15 they were being managed by their neurologist or
16 primary doc or a movement specialist in trying to
17 manage this. And yet despite trying these
18 medicines, still had significant psychosis that
19 impacted the daily lives.

20 DR. BRENT: Dr. Fahn?

21 DR. FAHN: Stan Fahn, Columbia University.

22 I have a couple questions. The first is for

1 Dr. Stankovic, and you may have touched on this in
2 one of your last answers. And that is, the effect
3 size, is there any difference in the effect size,
4 depending on the severity of the psychosis? In
5 other words, the more psychotic they are, severe,
6 is it a better effect size, or less, or what?

7 DR. STANKOVIC: Yes, we did that analysis
8 with a cutoff of 14 patients that had less than 14
9 on the SAPS-PD scale and more than 14.

10 Slide up, please. As you can see, that's
11 baseline SAPS-PD over 14 in the second to last line
12 and baseline SAPS-PD of patients less than 14.
13 Now, this is an arbitrary cutoff mostly based on
14 our feeling of what some moderate to mild -- or
15 actually moderate to more severe difference would
16 be. But we do see the patients with SAPS-PD less
17 than 14 did somewhat better on average.

18 DR. FAHN: Okay. And the second question,
19 I'm intrigued about this assessment system of
20 centralized evaluators. Is this a standard
21 operating procedure for psychiatric drugs? Is this
22 something new? Is this the first study ever

1 presented this way? Where does it fit into the
2 spectrum of how to analyze these drugs?

3 DR. STANKOVIC: It is a fairly standard
4 procedure. There is a whole industry of
5 organizations that actually perform different
6 reliability, or rating, or over-rating, or review
7 of rating of different scales.

8 So different companies do that differently.
9 Some provide that based on audiotape, and then the
10 centralized rater is listening to those tapes or a
11 portion of those tapes. This is the most
12 comprehensive method by us really having a
13 centralized rater doing a live video feed.

14 But it is done, and it has been done in
15 different trials. And I'm sure that colleagues
16 from the FDA may give some examples of drugs that
17 are approved on the basis of this exact
18 methodology.

19 DR. FAHN: It seems to me that it might
20 reduce variability because if you had a different
21 evaluator at each of the 56 sites, their standards
22 may have been different, and so this may be very

1 intriguing. Thank you.

2 DR. BRENT: Dr. Pickar?

3 DR. PICKAR: Just quickly, did you make
4 reference to prior to entering the study, patients
5 were on antipsychotics, and then you withdrew them,
6 and then gave, what, 3 weeks or 4 weeks like that?
7 What percentage of patients had been treated for
8 their psychosis with antipsychotics and then had
9 been removed from them before entering the study,
10 and how does that interact with findings?

11 DR. OWEN: Dr. Stankovic on the entry
12 criteria. One moment.

13 DR. STANKOVIC: Yes. Slide up, please.
14 This is the proportion of patients that were on
15 prior antipsychotic. The requirement of the
16 protocol was that within 5 half-lives or 3 weeks
17 prior to clinical trial, the patient would not be
18 on an antipsychotic.

19 Most of the patients, as we heard
20 previously, were on quetiapine, a few on Clozaril,
21 but this is the proportion, a smaller proportion,
22 of about 14 percent of the patients were on prior

1 antipsychotic.

2 DR. PICKAR: Where I'm going with it is, did
3 that in any way influence response rates, what
4 David just asked me. And that's what I'm trying to
5 sort this out; a lot of meds, a lot of moving parts
6 here.

7 So a third of the patients, not quite, had
8 been on antipsychotic when you accepted them into
9 the study. The drug could be out of their system,
10 but relapse time does not necessarily correlate
11 closely to the drug blood level. It could take a
12 while. It just makes them a little bit unstable.

13 I'm curious if you would analyze the data
14 vis-à-vis this as a factor, do you see any signal?

15 DR. STANKOVIC: Right.

16 DR. PICKAR: Going back to my earlier
17 schizophrenia question, there's a lot here.

18 DR. STANKOVIC: We did analyze the data.
19 However, there is relatively small proportion of
20 patients that were on prior antipsychotic. Slide
21 up. So the confidence intervals are somewhat
22 larger. But the patients that were on prior

1 antipsychotics, actually, our point estimate was
2 better than --

3 DR. PICKAR: They did better.

4 DR. STANKOVIC: -- the patients that were
5 not on prior antipsychotic, yes.

6 DR. PICKAR: Right --

7 DR. STANKOVIC: But again, I mean,
8 confidence intervals are really, really wide
9 because we have relatively few patients that were.

10 DR. PICKAR: Right.

11 DR. BRENT: Did you have an additional
12 comment?

13 (No response.)

14 DR. BRENT: I think that concludes this part
15 of the program. We'll take a 15-minute break, and
16 we'll come back at 10:55. And remember, we
17 shouldn't discuss this amongst ourselves.

18 (Whereupon, at 10:40 a.m., a recess was
19 taken.)

20 DR. BRENT: We're now going to proceed with
21 the FDA presentation. Thank you. Please take your
22 seats.

1 **FDA Presentation - Paul Andreason**

2 CAPT ANDREASON: Good morning, and welcome
3 back from the break. I'm Dr. Paul Andreason with
4 the FDA. I'm the clinical reviewer for NDA 207318,
5 pimavanserin for the treatment of psychosis
6 associated with Parkinson's disease.

7 Just to provide a little bit of context, I
8 was previously with the FDA from 1995 to 2006 and
9 had left for a period of eight years doing some
10 other things. And so upon my return, I was
11 assigned this NDA.

12 The reason I give that context is because I
13 was one of the reviewers involved with the
14 treatment of psychosis and agitation associated
15 with Alzheimer's disease. And in those reviews, we
16 found some rather alarming serious adverse events
17 and deaths that were disproportionate in the
18 treatment groups. And I regret to say that we have
19 found a similar signal with pimavanserin.

20 I agree with the sponsor, with Acadia, that
21 psychosis associated with Parkinson's disease is a
22 valid treatment target and that there are a

1 significant number of people who will suffer from
2 Parkinson's disease psychosis. One study estimates
3 that approximately 50 percent of patients with
4 Parkinson's disease will suffer psychosis.

5 I believe that the company has met the
6 standard of evidence that was previously agreed to
7 with the agency in that data from a single,
8 strongly positive study, study 020, with supportive
9 safety and efficacy data from an earlier trial
10 would be sufficient to review for this NDA.

11 For those who may be joining us newly and
12 did not hear the full presentation from Acadia, the
13 data comes from mostly study 020 as there were four
14 total controlled trials, one of which was positive.
15 And this is not new to the FDA or drug development.
16 There are frequently trials that fail, and we
17 always take this into account. But this is not
18 necessarily unique.

19 So today what I would like to focus on in my
20 presentation is a brief review of efficacy of the
21 one positive controlled trial. We also did an
22 exploratory analysis of Parkinson's disease

1 patients in the 6-week controlled trial pooled
2 data, though this is not a basis for approval. I
3 just want to make that clear. It was an
4 exploratory analysis. And then, we did an analysis
5 of safety and exposures with particular focus on
6 the controlled trial data and the 6-week controlled
7 trial data as well as study 020 as a standalone.

8 The efficacy evaluation of study 020 is such
9 that it did show that there was evidence of
10 efficacy. The completion rates were adequate, and
11 there were comparable number of patients who
12 completed in each study.

13 What I'd like to also kind of make clear is
14 that the numbers that we're dealing with in this
15 development program are relatively small. And so
16 though there are a small number of adverse events
17 and disproportionate numbers of deaths, there's
18 also a small number of patients involved in the
19 clinical trial itself. And the statistical
20 significance of the study hinges on small numbers
21 of patients as well.

22 The primary endpoint was the nine items of

1 the 20 item Schedule for the Assessment of Positive
2 Symptoms, originally designed for schizophrenia by
3 Nancy Andreasen and published in Iowa in 1984. And
4 each item is scored from zero to 5. As was pointed
5 out earlier, the score could go from anywhere
6 between zero and 45 with an average entry score of
7 15. And the rater for the SAPS-PD was the central
8 rater.

9 Now, the secondary endpoint was the CGI, and
10 each of those was done by a local rater, so
11 independently.

12 Here's a breakdown of the SAPS-PD that
13 you've already seen so that there are three items
14 on the delusional scale as well as a global item
15 and four items on the hallucination scale with a
16 global item.

17 This slide shows you that the primary
18 efficacy variable was met in that there was a
19 statistically significant difference between
20 pimavanserin and placebo with respect to the
21 SAPS-PD, the difference being a decrease in
22 3 points on the SAPS-PD, which equates to about a

1 23 percent difference.

2 But this is a mean difference, and I'd like
3 to underline that mean differences in clinical
4 trials do not necessarily correlate with clinical
5 significance, either. And perhaps looking at
6 different response rates, as Acadia and as we did
7 as well, will flesh out what the clinical
8 significance of the response is a little bit better
9 than just looking at mean data.

10 The secondary clinical efficacy endpoint was
11 the CGI, which was also statistically significantly
12 different from placebo, and I agree with that. I'd
13 just like to point out also that p-values are tests
14 of the probability and that any particular finding
15 is by chance. It doesn't necessarily reflect the
16 magnitude of the effect, though it may.

17 So we have fairly small p-values, which is
18 good. It lets us know that these findings are not
19 by chance. But it doesn't necessarily reflect the
20 magnitude of any particular effect.

21 Over time, this is how patients respond with
22 respect to symptoms of psychosis between

1 pimavanserin 34 milligrams and placebo. Separation
2 is evident at week 4 in study 020. The trials were
3 designed to be 6-week trials because the separation
4 was observed to be greater at week 6 than week 4.
5 And in drug development, one wants to provide proof
6 of the principle that the drug is superior to
7 placebo. And I believe that Acadia has presented
8 data to support that it is superior to placebo with
9 respect to treating psychosis.

10 Now, the safety evaluation of the
11 development program includes the following patient
12 population. There's a total that I reviewed, and
13 as time has progressed, there are more total
14 exposures. 1,096 total patients were exposed, 625
15 of whom had Parkinson's disease or Parkinson's
16 disease psychosis. And 177 had schizophrenia; 294
17 were normal volunteers.

18 So there were 764 exposures to
19 34 milligrams, and then various other doses that
20 were greater than 34 milligrams. But the trial,
21 the controlled trial used the dose of
22 34 milligrams.

1 In the safety evaluation, there were 498
2 total patients with Parkinson's disease psychosis
3 that were exposed to pimavanserin. Two hundred-two
4 patients with Parkinson's disease psychosis were
5 exposed to the 34-milligram dose, and 231 in
6 placebo during the 6-week controlled trial
7 experience.

8 I really do want to focus on the 6-week
9 controlled trial experience for deaths, serious
10 adverse events, and severity of adverse events
11 because, as Acadia pointed out, this is a medically
12 frail population. And the rates of illness in the
13 general population in the open label trial don't
14 really tell us very much about the effect of the
15 drug by itself because, as I said and as we
16 observed, the adverse events that we have seen are
17 commensurate with the types of things that we see
18 with advanced Parkinson's disease.

19 Just to show this, 459 patients received
20 long-term open-label pimavanserin treatment. There
21 were 51 deaths in open-label treatment, which is
22 about 11 percent. And this is in kind of the

1 ballpark that you see in the literature for
2 open-label or extended treatment in studies of
3 Parkinson's disease psychosis.

4 So again, the safety focus of my review was
5 the 6-week controlled trial data looking at deaths,
6 serious adverse events including deaths, and severe
7 adverse events.

8 Now, deaths and serious adverse events
9 analyzed as a group is part of our standard
10 exploratory analysis in the NDA review.

11 So in the review of the serious adverse
12 events including deaths, what we found was that
13 there was about a 2.4-fold increase in the observed
14 risk ratio between pimavanserin and placebo.

15 The deaths and serious adverse events
16 observed with pimavanserin did not have a readily
17 apparent unifying mechanism as was previously
18 stated, and this is consistent with what we've
19 observed with the antipsychotics in the development
20 programs for Alzheimer's dementia and agitation.

21 Now, this presents us with a bit of a
22 dilemma as regulators because on the one hand, we

1 have evidence that the drug is superior to placebo,
2 and at various levels of exploring clinical
3 efficacy, it continues to be superior to placebo,
4 whether it's complete response, 50 percent
5 response, point reduction. All of these show that
6 there is a treatment effect. However, there is the
7 disproportionate number of deaths and serious
8 adverse events.

9 FDA has not approved an antipsychotic drug
10 with this safety signal for use in the agitated,
11 psychotic for demented elderly populations.

12 However, previously when these applications came to
13 us, the drugs that were under review were already
14 on the market. If we follow our usual logic and
15 didn't approve pimavanserin for the treatment of
16 Parkinson's disease psychosis, it couldn't be used
17 off label. It wouldn't be available. So that is
18 our dilemma from a regulatory point of view.

19 So just to review, and these numbers are
20 exactly the same that you saw presented by Acadia,
21 in the placebo group, there was 1 death versus
22 3 deaths in the pimavanserin 34-milligram group.

1 And these comparisons are only between placebo and
2 pimavanserin 34 milligrams. Serious adverse events
3 were 8 versus 16. And the severity of the adverse
4 events did appear to be somewhat dose related.

5 Just to give you an idea of what those
6 adverse events represented, I've coded them by
7 color. Black are mental status changes. Green
8 appear to be mostly infectious, and then red,
9 cardiovascular. And blue, I've coded pretty much
10 as other.

11 So this represents the 16 cases. There were
12 3 urinary tract infections that I've grouped
13 together. The cases that resulted in fatality are
14 noted in parentheses with fatal. The one case of
15 headache actually was hospitalized with delirium
16 and died 74 days later. It was not counted among
17 the deaths because the death occurred more than
18 30 days after the discontinuation of the drug.

19 These represent the placebo cases, and you
20 can see by the color coding, that the
21 disproportionate numbers of serious adverse events
22 occurred in the mental status changes and

1 infections. And this graph kind of highlights
2 those differences: 5 versus 2 in the mental status
3 changes, 6 versus 2 in the infectious, with a rough
4 equivalence between cardiovascular and other.

5 So approval of pimavanserin would hinge on
6 whether or not the efficacy is warranted in the
7 face of a safety signal. So we thought about
8 different ways of exploring clinical meaningfulness
9 versus risk. The way that I thought helped
10 demonstrate this the most was using the
11 calculations of number needed to treat and number
12 needed to harm.

13 This is also a responder analysis looking at
14 the 6-week controlled trial data, and I just want
15 to say that looking at the -- I beg your pardon.
16 This is still study 020. This goes right along
17 with what Acadia presented. This is our analysis,
18 and I think it's exactly the same.

19 We used nominal p-values instead of the
20 calculated p-values because they were not the
21 a priori designated primary efficacy variables, but
22 they're less than .05.

1 This represents the efficacy data on those
2 same factors in the pooled data, and they still
3 show statistical significance. But the response
4 rates are a little bit different because it
5 involves more patients. In the 100 percent
6 response rate, there were 13, 14 percent of
7 patients on pimavanserin that had a complete
8 response, and that's roughly equivalent to study
9 020. However, there was a greater placebo
10 response. There was 7 versus 1 percent.

11 The CGI response is a little bit different
12 but roughly equivalent.

13 This graph shows what the distribution of
14 responses are on the SAPS-PD scale in the 6-week
15 trial, and it shows that on basically all
16 responses, and there is a greater number of
17 patients who have a better response on pimavanserin
18 versus placebo. There are some patients who become
19 clinically worse taking pimavanserin, and there are
20 a number of patients who become clinically worse
21 taking placebo.

22 The number of patients who were clinically

1 worse on placebo on the SAPS-PD is greater than in
2 pimavanserin. But if you focus on effectiveness,
3 the numbers show that pimavanserin continues to be
4 effective if you look at 3-point reductions, 5-
5 point reductions or 7-point reductions.

6 But given the safety scale, we wanted to
7 look at responses that would be clinically
8 significant and that it would keep people out of a
9 nursing home because it turns out that extended
10 care facility placement is what seems to correlate
11 with an increased risk of mortality as opposed to
12 the symptoms themselves. But if they cannot be
13 managed except in an extended care facility, that's
14 when the risk of death and serious morbidity goes
15 up.

16 So we felt that a 50 percent reduction or a
17 5-point reduction in the SAPS-PD might be more
18 significant, or a 7-point reduction. And we saw
19 that at all of these levels, there was a difference
20 in treatment. But how would this stack up against
21 the observed risk that we saw with serious adverse
22 events? So again, I used numbers needed to treat,

1 and here's the reference for that.

2 Just to outline that, numbers needed to
3 treat is an epidemiological measure in
4 communicating the effectiveness of a healthcare
5 intervention, typically, a treatment with
6 medication. And it's the average number of
7 patients who need to be treated for one to benefit
8 in a controlled trial compared with placebo, and
9 it's defined as the reciprocal of the absolute risk
10 reduction.

11 So these are the factors that go into
12 calculating numbers needed to treat. And here's an
13 example of calculating one number needed to treat,
14 and we discussed that we would be doing this kind
15 of a presentation. You saw the numbers needed to
16 treat presented by Acadia. We have the same
17 numbers. We've come up with the same numbers.

18 So for a response of much or very much
19 improved, which we thought would be a significant
20 improvement to keep somebody out of a nursing home,
21 you needed 5 patients treated in order to have the
22 response be due to drug.

1 Here are some different numbers needed to
2 treat calculated in study 020 and in the pooled
3 population based on different response rates. For
4 a 50 percent reduction in symptoms, according to
5 study 020, you'd need 11 patients treated, 15 in
6 the pooled data, 30 percent reduction, which would
7 be considered a minimal clinical significant
8 difference.

9 We're not sure that that would preclude
10 someone from being admitted to a nursing home, but
11 7 versus 5. Full response, which would be very
12 significant, 8 in study 020 versus 13 in the pooled
13 population, and a CGI score of improved or very
14 much improved, 5 versus 8.

15 Now, calculated numbers needed to harm based
16 on two definitions: one, death and the other one,
17 serious adverse events including death. For the
18 pooled population, 16 out of 202, or roughly
19 8 percent, versus 3 and a half percent, the number
20 needed to harm is 23. For death using the pooled
21 data, the number needed to harm is 91.

22 For study 020, the number needed to harm

1 where death is the definition of harm is 100
2 because you have 2 patients out of 95 that died in
3 the pimavanserin treatment group versus 1 in the
4 placebo group, so that ends up being a number
5 needed to harm of 100. If you use serious adverse
6 events, including death in study 020, it's 11.7
7 percent versus 4.4. The number needed to harm is
8 14.

9 Now, to look at clinical meaningfulness in
10 risk versus benefit, I divided the number needed to
11 harm by number needed to treat, and that will come
12 up with the number of patients for each response
13 that you wish to achieve the number of patients
14 that will suffer that particular harm, whether it's
15 death or serious adverse events.

16 If, for example, the number needed to harm
17 is 100 and you only needed to treat 2 people to get
18 a response, that ratio would be 50 to 1. However,
19 if the number needed to treat goes up to 10 and the
20 number needed to harm remains constant at 100 for
21 every 10 responses, you get one event that is a
22 death or a serious adverse event. So again, the

1 two definitions of harm, death and serious adverse
2 event, and the number needed to treat is based on
3 whatever response level you wish to look at.

4 The number needed to harm to number needed
5 to treat comparison for a 50 percent reduction in
6 the SAPS-PD with number needed to treat being 11,
7 looking at 100 being the number needed to harm for
8 death, you get 9 responses and 1 death. For a
9 30 percent response, the number needed to treat is
10 lower, 100. So for 14 responses, you have 1 death.
11 For a full response, 100 to 8, so 13 responses and
12 1 death and a CGI score of improved or much
13 improved, 20 responses and 1 death attributable to
14 drug.

15 If we look at serious adverse events
16 including death for a 50 percent reduction, you get
17 3 responses for 2 serious adverse events;
18 30 percent, 5 responses for 2 serious adverse
19 events. Full response, 2 responses for 1 serious
20 adverse event and an improvement of the CGI; much
21 improved or improved, 3 responses for one serious
22 adverse event. This is looking at study 020 data.

1 If we look at the pooled data where the
2 number needed to harm for death is 91, number
3 needed to treat for a 50 percent reduction is 15,
4 6 responses, 1 death; 30 percent, 18, 1 death; full
5 response, 7 responses, 1 death; CGI of improved or
6 much improved, 10 responses, 1 death.

7 These are the numbers for serious adverse
8 events: 3 responses, 2 serious adverse events for
9 a 50 percent reduction; full response, 7 responses,
10 4 serious adverse events; and a CGI of improved or
11 much improved, the number needed to treat is 9, and
12 so you get 5 responses, 2 serious adverse events.

13 In summary, you need to treat 91 people to
14 get 7 full responses. You'll have 5 serious
15 adverse events based on these numbers, one of which
16 will result in death. And to get a CGI improvement
17 of 10 patients, you have to treat 91, 4 of whom
18 will have a serious adverse event, one of which
19 will result in death.

20 Questions?

21 **Clarifying Questions to FDA**

22 DR. PICKAR: I don't have a feel for what

1 those kind of statistics would look like for
2 antipsychotic drugs, for a frame of reference?

3 CAPT ANDREASON: For a frame of reference, I
4 looked at clozapine, and I only looked at the
5 published material. I don't have raw data from
6 clozapine.

7 But if you'd bring up slide number 3,
8 please. I beg your pardon, the backup slides, and
9 if you'll go to the next slide, please.

10 There was not a lot of information provided,
11 but in the controlled trials of clozapine and
12 placebo in Parkinson's disease psychosis, and these
13 were 4-week controlled trials, there were no
14 deaths, 3 dropouts. And in the U.S. study, the
15 serious adverse events were not necessarily
16 described as such, but the decrease in CGI severity
17 of 50 percent -- excuse me -- of 2 or greater,
18 decrease of the CGI severity of 2 or greater, there
19 were 15 out of 30 in the clozapine group, 5 out of
20 30 in the placebo group. So number needed to treat
21 there was 3.

22 Now, if you'll go to the previous slide,

1 please, and you look at -- your question was
2 serious adverse events in our experience with other
3 drugs; is that right?

4 DR. PICKAR: Yes. I'm sorry. Yes.

5 CAPT ANDREASON: Okay. So in this study as
6 well, there were no deaths. Serious adverse events
7 in the placebo group outnumbered those in the
8 treatment group.

9 DR. PICKAR: Because I'm not used to dealing
10 with that kind of a parameter, from this point of
11 view, this is less -- I hate to use the simple
12 word -- dangerous --

13 CAPT ANDREASON: In the 4-week controlled
14 trial. Now --

15 DR. PICKAR: In the context of that trial,
16 that's correct --

17 CAPT ANDREASON: Yes, right.

18 DR. PICKAR: -- considerably less at risk or
19 potentially harmful than pimavanserin.

20 CAPT ANDREASON: These are not directly
21 comparable, but yes.

22 DR. PICKAR: Okay.

1 CAPT ANDREASON: So other questions?

2 DR. SCHMID: I have two questions. One is
3 on your slide 3. I'm wondering what's the natural
4 variability, if you know it, of this new scale
5 because the two groups are a little bit different
6 at baseline. One moves a little bit more than the
7 other, but how much of that might be regression to
8 the mean? So that's my first question.

9 My second question is if you have any
10 measures of uncertainty on these number needed to
11 treat and number needed to harm?

12 CAPT ANDREASON: Oh, I don't. I could have
13 come up with confidence intervals for you, but I
14 don't have those right with me.

15 They're broad. I mean, I can tell you that
16 they're very broad because the numbers are small.
17 So these are estimates based on the data that we
18 have.

19 Variability in the rating scale, as in
20 general, this is the first time the SAPS-PD has
21 been used, so I can't comment on general
22 variability. But I can say that we actually did an

1 analysis of the SAPS 20-item scale, and
2 pimavanserin was superior to placebo on the 20-item
3 scale.

4 So unlike the other three studies, it did
5 show superiority on a scale that they used in a
6 previous study. I don't know whether that helps
7 answer your question.

8 DR. SCHMID: So what I was trying to get at
9 was how much will this scale -- if you measure it
10 on different days or different weeks, how much
11 would it change? I mean, you're saying these
12 changes aren't that big.

13 CAPT ANDREASON: Day-to-day variability.

14 DR. SCHMID: Day-to-day variability, right.

15 CAPT ANDREASON: Perhaps Acadia can answer
16 that question.

17 DR. STANKOVIC: We do not have day-to-day
18 variability on the scale. Visits are done in the
19 program on a weekly basis. But the overall
20 variability is within what was anticipated and in
21 the assumption of the trial.

22 DR. SCHMID: So I mean, you have a 3-point

1 change. Even on a week-to-week variability, is
2 that something you might expect to see naturally in
3 some people or?

4 DR. STANKOVIC: Three points change on the
5 individual level, possibly, I mean, but we don't
6 have data to confirm that one or the other way.
7 But I mean, we are talking -- always we talk
8 placebo subtracted change versus individual change,
9 and these are two different categories in terms of
10 how one looks at the effect of the drug.

11 Obviously, the change that would be
12 attributed to the treatment, obviously is placebo
13 subtracted. But in terms of the individual
14 variability of the patients and change for
15 individual patients we have, these are different,
16 larger numbers, obviously.

17 CAPT ANDREASON: Could you go back to my
18 original slide deck, please?

19 I think maybe to answer your question, there
20 was a fair amount of placebo response. And if you
21 look at 3-point changes versus 5-point changes, you
22 see that the placebo response goes up and down

1 based on how you parse out the different types of
2 responses you want to look at. And I think that
3 that lets you know kind of on an individual basis
4 what that variability might be. But we do look at
5 drug versus placebo, and it does separate.

6 DR. BRENT: Dr. Winterstein?

7 DR. WINTERSTEIN: Slide 18, that was in
8 follow-up to a comment that the sponsor made to
9 Dr. Gerhard, and I just wanted to get your take on
10 this. So your slide 18, if you could bring that up
11 again.

12 CAPT ANDREASON: Sure.

13 DR. WINTERSTEIN: On this slide, you show
14 the various rates of adverse events, serious
15 adverse events as well as compiled adverse events.
16 And the compiled adverse events, obviously, the
17 difference is diluted between the drug and the
18 placebo group, and the sponsor commented that this
19 might be the better or the more comprehensive way
20 to look at those data.

21 I was curious to hear from you or I was
22 curious about your comment. I mean, my

1 interpretation would be typically any type of
2 adverse events includes placebo responses in both
3 the placebo group and the treatment group like
4 headaches and nausea and vomiting and what have
5 you, which are not drug related. So you add a lot
6 of noise to an effect, and by adding noise, the
7 effect gets diluted.

8 So I would be very worried to look at the
9 any adverse event rates and conclude that this is
10 reassuring, that there really is not a problem.
11 And I would go back and focus on the serious
12 adverse events, and I was curious how you would
13 interpret the sponsor's comment on that.

14 CAPT ANDREASON: Well, we do have some
15 history with that, and this is the type of thing
16 that we saw with the adverse event profiles in the
17 antipsychotic use in the Alzheimer's patients. And
18 Dr. Stone is going to present the history on that
19 and the analysis as well, looking at death.

20 Looking at serious adverse events this way
21 and deaths is kind of part of our standard way of
22 looking at drugs across the board. So I noted

1 Acadia's disagreement with the way that I looked at
2 it, but again, this is a standard way of looking at
3 it. This is not a novel, exploratory way of
4 looking at it.

5 DR. WINTERSTEIN: Then I had one extra
6 question, which wasn't addressed in my first bunch
7 of questions, so I thought I'd ask it here, if I
8 may. This was slide 25.

9 CAPT ANDREASON: Twenty-five?

10 DR. WINTERSTEIN: Yes. The sponsor had
11 characterized the enrolled patients in study 020 as
12 patients who have moderate to severe psychosis, and
13 I had asked whether that would really be an
14 appropriate characterization of those patients
15 considering that their SAPS scale is anchored at
16 zero to 45 and the average entry criteria was 15,
17 which to me, again, doesn't sound like this is
18 moderate to severe. That sounds mild.

19 I still don't know the distribution of
20 patients who were enrolled. We only see the
21 average of 15, but looking at the responses in the
22 treatment group, we have nobody with a response

1 higher than 18, which would suggest that either
2 there really are no patients who had a severe form
3 of psychosis as rated on this scale.

4 So do we actually know how good the response
5 was, and we had that one subgroup analysis that
6 had --

7 CAPT ANDREASON: The range of entry scores
8 went from 6 to 33, if I'm correct. I'm getting a
9 nod from Dr. Stankovic.

10 DR. WINTERSTEIN: Okay.

11 CAPT ANDREASON: And I don't have the exact
12 distributions of those scores. He did the 14
13 versus under 14. But again, they do show efficacy.

14 DR. WINTERSTEIN: In a group of patients who
15 has a milder form of psychosis. I'm just trying to
16 establish what type of population --

17 CAPT ANDREASON: Right, these were --

18 DR. WINTERSTEIN: -- because the last talk
19 from the sponsor talked a lot about impact, and it
20 characterized patients who had repeated, massive,
21 severe hallucinations and delusions every day. And
22 I don't see these patients reflected in this trial.

1 So I'm just trying to figure out which patients
2 were actually studied.

3 CAPT ANDREASON: These are patients, for the
4 most part, who had caregivers. And I think the
5 goal of treatment is to keep people from entering
6 an extended care facility. So they're not going to
7 be by design terribly ill, but ill enough that
8 they're kind of on the verge of needing extended
9 care treatment.

10 So in my review of it, I think that it was
11 an appropriate patient population. Even though by
12 the numbers, it doesn't look that bad, it's
13 significantly bad enough to answer the question, I
14 believe.

15 DR. BRENT: Dr. Gerhard?

16 DR. GERHARD: Well, I pretty much had the
17 same question as Dr. Schmid, and I already know the
18 answer, that we don't have confidence intervals for
19 particularly the number needed to harm estimates.

20 So maybe in the absence of this, if we could
21 look at the slide 38 just as an example. I think
22 it's important to realize what the impact is of

1 just a single event. So if we take the first
2 measures, 9 responses in greater 50 percent
3 reduction of SAPS-PD versus 1 death -- and this is
4 just back of the envelope -- I think one more event
5 in the placebo versus the treatment group probably
6 would shift this from around 14 to 1 versus 5 to 1.

7 So I think that's obviously not a formal way
8 to think about the uncertainty, but just kind of to
9 give some perspective what a single event would do
10 to these estimates, which are very helpful. But I
11 think it's important to be aware of the degree of
12 uncertainty given the small numbers here.

13 CAPT ANDREASON: Absolutely. There's a high
14 degree of uncertainty because the numbers are very
15 small. That said, if you look at the 16 versus 8
16 serious adverse events, that had a p-value of
17 .05 -- so there's only a 1 in 20 chance that that's
18 by chance.

19 So again, the p-values help us know kind of
20 maybe what the chances are, that it's just a chance
21 finding. And I don't believe it's a chance
22 finding. This is very similar to what we see in

1 the other antipsychotics.

2 DR. GERHARD: So I think my comment, just a
3 quick response, was less about whether it's a
4 chance finding or not, that there is an increased
5 risk of harm. In the trade-off between benefit and
6 harm, the magnitude is really critical, obviously,
7 for both.

8 Obviously, we have uncertainty around the
9 benefit as well and probably quite a bit. But
10 particularly for the deaths and for some of the
11 adverse events, the uncertainty about the magnitude
12 I think is just very strong. And we need to be
13 aware of this when we make a consideration and a
14 decision.

15 CAPT ANDREASON: Correct. I think that's
16 what makes it a hard decision.

17 DR. BRENT: Dr. Grieger?

18 DR. GRIEGER: Maybe this has to do with the
19 distribution of the response rates, but it just
20 seems counterintuitive to me -- and this is on your
21 slide 31 -- that it only takes 8 patients needed to
22 treat to get a response at 100 percent response,

1 but it takes 11 patients to get a 50 percent
2 reduction? That just seems backward. I don't
3 understand how that --

4 CAPT ANDREASON: That's because of the
5 varying placebo response at each level.

6 DR. GRIEGER: Okay.

7 CAPT ANDREASON: Yes, and so for a
8 50 percent response, there was basically a
9 10 percent difference between drug and placebo.
10 There was roughly 37 percent had a 50 percent
11 reduction in drug versus 27 percent. And like I
12 said, I'm working from memory, but it's roughly
13 correct.

14 DR. GRIEGER: So the people who did really
15 well overrode the placebo effect.

16 CAPT ANDREASON: Correct.

17 DR. GRIEGER: Okay.

18 DR. BRENT: Dr. Morgan?

19 MS. MORGAN: So going along with you two,
20 this data that came to us says that -- I guess it
21 came from you, and I thought there was a
22 discrepancy. But it says one must treat

1 11 patients for one patient to receive a 50 percent
2 reduction. And then it says put another
3 way -- this is a ratio. So put another way, for
4 every two patients who achieve a 50 percent ratio,
5 one patient will experience a serious adverse
6 effect.

7 CAPT ANDREASON: That's correct.

8 MS. MORGAN: Okay.

9 CAPT ANDREASON: By my calculation there,
10 and that's the number needed to harm divided by the
11 number needed to treat.

12 MS. MORGAN: Right.

13 CAPT ANDREASON: Correct.

14 MS. MORGAN: Okay. Thanks.

15 DR. BRENT: Ms. Witczak?

16 MS. WITCZAK: To get breakthrough therapy
17 designation, just for context, what is a typical
18 number needed in a study? Because this is a pretty
19 small number, as you keep saying, in this study.
20 When I look at what they originally had done back
21 in the original, it was a greater number in the
22 original studies that did not meet clinical

1 significance with the placebo effect.

2 So just out of context, what is the FDA's
3 rule of thumb when you grant a company breakthrough
4 therapy designation for number of participants?

5 DR. TEMPLE: There's no rule. Breakthrough
6 comes when the putative benefit is something that
7 isn't otherwise available so that's one thing. And
8 it can be quite a small study if it shows an
9 impressive effect.

10 For example, in oncology where a lot of the
11 breakthrough things are, if you take a bunch of
12 people who failed prior therapies and get tumor
13 responses in 8 or 9 people, that might be very
14 impressive.

15 We don't necessarily insist on statistical
16 significance, but usually we do. And it can be on
17 an early marker of benefit; it doesn't have to be
18 on the final outcome. But in some cases, it's been
19 quite small trials with impressive results. So
20 there's no rule. And then other times, you see we
21 get presented with the results of a modest sized
22 controlled trial. But the benefit has to be

1 something that's not otherwise available.

2 Can I ask a question also of Paul?

3 DR. BRENT: Sure.

4 DR. TEMPLE: The list of treatment emergent
5 SAEs on your slide 19 includes some things that
6 look potentially irreversible and dangerous and
7 some things where presumably it would go away if
8 you stopped the therapy.

9 Have you done your number needed to treat
10 and number needed to harm looking at those
11 separately? I mean, for example, change in mental
12 status, presumably that goes away as soon as you
13 stop the drug, not necessarily a big deal, whereas
14 a bad infection could lead to something.

15 Any distinction of those? I just wondered
16 if you'd done any analyses of breaking the bad
17 effects into subsets?

18 CAPT ANDREASON: Well, given that the
19 numbers are so small, it kind of got to the point
20 where I couldn't figure out which ones to pull and
21 not.

22 DR. TEMPLE: Okay.

1 CAPT ANDREASON: For example, some of
2 them -- and this is where Acadia had a bit of
3 disagreement. Their number needed to harm, as I
4 recall, for a dropout was 27. That sounds
5 reasonable based on --

6 DR. TEMPLE: That was because some of the
7 people who had those effects stayed on therapy.
8 They said that earlier.

9 CAPT ANDREASON: Right.

10 DR. TEMPLE: Okay.

11 DR. BRENT: Dr. Fahn?

12 DR. FAHN: I think we should also consider
13 the adverse events that are more common in the
14 placebo group, falls and orthostatic hypotension.
15 In other words, is it the active drug is causing
16 less falls and less orthostatic hypotension? I
17 mean, are these benefits?

18 These two symptoms are particularly
19 important in people with Parkinson's. Every visit,
20 every patient gets asked this question. We check
21 their blood pressures every time they come. Our
22 drugs like levodopa and other dopaminergic agents

1 tend to cause orthostatic hypotension. The disease
2 itself causes orthostatic hypotension. If we had
3 something that reduced that, it'd be terrific.

4 So to me, although they're not serious
5 adverse events like this list here, they are
6 potentially serious events for our patients and
7 very common in this population and in Parkinson's
8 because they lose balance anyway in Parkinson's.

9 So we consider these extremely important.
10 If anything does less of it, that's to our view a
11 benefit. I think that should be considered also.

12 CAPT ANDREASON: All right.

13 Now, these are the lists of the serious
14 adverse events that occurred in the placebo group,
15 and you'll notice that there's a spinal fracture
16 and decubitus ulcer. The spinal fracture could be
17 attributed to a fall, whereas the worsening of
18 Parkinson's disease in the treatment group and the
19 breast cancer patient, again, I coded those as blue
20 because they're other.

21 So you could argue that the spinal fracture
22 was due to a fall where there was no fall in the

1 serious adverse events that were experienced on
2 drug.

3 Anyway, I do need to give time to Dr. Stone
4 for his context of the antipsychotic drugs.

5 Are there any other questions that pertain
6 specifically to mine? We'll have time to have more
7 questions to me as well.

8 (No response.)

9 CAPT ANDREASON: Good. Thank you very much.

10 **FDA Presentation - Marc Stone**

11 DR. STONE: Good morning. We're here today
12 to discuss drug treatment of organic psychosis, and
13 we've had some experience with that in the past.
14 And the result of that experience was this box
15 warning, that "elderly patients with
16 dementia-related psychosis treated with
17 antipsychotic drugs are at increased risk of death,
18 and that antipsychotics are not approved for the
19 treatment of patients with dementia-related
20 psychosis."

21 How did we come to this conclusion? We
22 looked at 17 studies that were submitted to us for

1 the treatment of psychosis and dementia. There was
2 a variety of drugs involved, sometimes as the
3 primary drug, sometimes as an active control. And
4 you see a pretty broad range of drugs, although
5 maybe we should note that clozapine was not among
6 them.

7 In total, there were 5377 subjects, about
8 twice as many on drug as placebo. The average age
9 was 71, approximately 95 percent between 66 and 96.
10 So a group that's a little bit older than what we
11 saw here in the pimavanserin studies, but roughly
12 similar.

13 There are a number of different ways of
14 measuring this. I think the most useful one is
15 death within 30 days of the intended treatment
16 period. You don't want to look at deaths within a
17 certain period of the end of actual treatment
18 because you're dealing with a frail population
19 where a drug, for example, could not be tolerated
20 in the frailest people. That person's taken out of
21 the trial. They die for some unrelated reason. If
22 they had stayed in the trial, it would have counted

1 as a death in the trial, which may well have
2 happened if they had been on placebo.

3 So we looked at the deaths within 30 days of
4 the intended treatment period. We looked beyond
5 the intended treatment period because, again, the
6 deaths in these patients are usually not very
7 acute. It's usually some kind of insult that leads
8 to infection, and then after a few days or a few
9 weeks, the patient dies.

10 We were pretty confident that the
11 investigators in clinical studies would know that a
12 patient had died within 30 days -- within this
13 period. And we did some exploratory analysis to
14 show that that was pretty consistent. For example,
15 we didn't see any decline in the death rate among
16 placebo patients and seemed to be very consistent
17 along that period of time.

18 However, it really wasn't important. We got
19 almost exactly the same results using different
20 other analytic periods, but I think this 30 days is
21 probably the more comprehensive picture.

22 I think when we're just looking at these

1 studies, we're sort of noticing that there were a
2 few more deaths in the treatment arm. And, again,
3 we're dealing with a frail and elderly population.
4 It wasn't too surprising to see some deaths in each
5 arm, and there were always a few more. It didn't
6 look statistically significant.

7 But there was a remarkable consistency when
8 we looked at all the trials at the same time. And
9 if you want to do a simple, intuitive back of the
10 envelope way of analysis, there were 30 randomized
11 comparisons of drug and placebo. And if you flip a
12 coin 30 times, it's going to come up 28 or more
13 heads or 28 or more tails, about one occurrence in
14 a million. So that seemed pretty unlikely.

15 So we did a formal analysis using random
16 effects Poisson regression to combine the trials in
17 a meta-analysis, and it gave us an incidence ratio
18 of 1.7, a 70 percent higher mortality rate with
19 those confidence intervals and clearly
20 statistically significant.

21 You can translate that into mortality rates,
22 which you can see here, about 141 deaths per

1 thousand patient-years with antipsychotic drugs,
2 83 deaths per thousand patient-years with placebo,
3 and those confidence intervals in parentheses and a
4 difference of 58 deaths per thousand patient-years.

5 We were talking about number needed to harm.
6 The difference in mortality rate was about 1 and a
7 half percent. So if you want to take death as your
8 sole harm, the number needed to harm would be about
9 60.

10 Here, you can see the various trials, and
11 again, they only have a couple of deaths in each
12 trial. Some had as many as a dozen, but you can
13 see the confidence intervals are very wide. The
14 point estimates, however, are almost always above
15 1. And then when you pool them, you get something
16 that looks pretty clear as an elevation.

17 For reference here, I put in pimavanserin.
18 Again, small number of deaths, very wide confidence
19 intervals but elevated. So it doesn't look any
20 different, but a few number of deaths, this could
21 mean anything. It could just be chance. But if
22 you want to use this as context or some kind of

1 prior, then you can say that this looks about the
2 same as the other trials.

3 Dose response, you can try to tease that out
4 by trying to come up with an equivalent dosage.
5 And there's a suggestion of dose response, but it's
6 not very strong. It's not statistically
7 significant. It's about a p-value of about 0.1,
8 1.15. Also, the analysis is done in a way that
9 kind of favors finding an effect.

10 So maybe when you're using the really high
11 dosage, you're seeing an effect; maybe not so much
12 among the lower doses. There's a suggestion there,
13 but not a really strong kind of dose response as
14 you might like to see in a pure pharmacological
15 kind of effect or analysis.

16 That brings us to the causes of death.
17 Here, these are ranked in terms of their
18 attribution. These are the excess rates of various
19 causes of death in the drug-treated group, and
20 these are excesses down below for placebo. These
21 lines represent confidence intervals for those
22 estimates.

1 We're dealing with around 200 deaths, but
2 when you start to break it down into different
3 causes, the numbers get small, the confidence
4 intervals get wide. But what you see is that even
5 the ones that seem to be -- where we can attribute
6 most of the mortality difference, which is you
7 would see over here, heart failure and pneumonia,
8 sudden death, sepsis, unknown, pulmonary embolism,
9 urinary tract infection, possibly a relation of the
10 big confidence intervals, they don't seem to be
11 related.

12 There doesn't seem to be any kind of common
13 physiological issue here, although I think we can
14 also be -- these definitions are fairly broad and
15 uncertain. For example, heart failure, most of
16 these cases were not your typical heart failure
17 case where the patient already has known pump
18 failure and they're on after load reduction and
19 digoxin and diuretics and what have you.

20 They may be incidentally that, but there
21 were mainly cases where somebody developed a
22 hypotension, and over a period of a week or two,

1 the hypotension was progressive. There was no
2 signs of infection, dehydration, blood loss,
3 anything that could explain it otherwise, and the
4 heart just seemed to be tottering out. Again,
5 these are anecdotal descriptions. There was a
6 variety of descriptions. A lot of these
7 descriptions were extremely vague and just said
8 heart failure, but those are classified there.

9 Similarly, sudden death, it wasn't your
10 classic somebody topples over in front of you, and
11 you put on the paddles and it reads ventricular
12 fibrillation, that kind of sudden cardiac death.
13 It was more along the order of, well, we went to
14 see this patient, and he looks fine and then came
15 back three hours later, and he was dead or he died
16 in his sleep, those kinds of things.

17 So it is kind of vague, but that's how the
18 results were skewed.

19 So this definitely seems to be an effect
20 here of increased mortality. What could be causing
21 it? Well, a physiologic process, again, you've got
22 a very broad, vague collection of causes of death,

1 and I would contrast it, for example, with
2 something like the Cox 2 inhibitors, where it was
3 clear that the excess mortality was coming from
4 myocardial infarction and other forms of arterial
5 thrombosis.

6 But I think you could also fairly ask
7 whether the diversity is real. These reports were
8 not blinded and adjudicated. They were submitted
9 by the site investigators, and sometimes with a
10 fair amount of detail and sometimes not very much
11 at all, but they're unblinded. And again, both for
12 the investigator and really the sponsor, their
13 principal concern is going to be with the people
14 that were treated with the drug. And they're going
15 to look at those cases carefully to try to tease
16 out whether they can see any drug effect there or
17 not.

18 If someone's on placebo or even on an active
19 control, they're not going to pay quite so much
20 attention. The patient died. It happens. This is
21 an elderly, sick person, so we don't know.

22 So it is possible that if there had been

1 better observation and data collection, we might
2 see less diversity in causes of death, and we might
3 have a little better sense of what's going on. But
4 again, this is speculation. And like I said, it
5 doesn't seem to fit any physiological or
6 pharmacological thing that we can just point at and
7 say, well, pimavanserin, for example, is different
8 in this way pharmacologically, so we shouldn't
9 expect this or something like that.

10 So to think a little bit outside the box,
11 what about something psychosomatic? There is a
12 certain amount of anecdotal evidence about a will
13 to live in patients, and it's possible that in
14 demented patients, it's manifested as psychosis or
15 behavioral problems and suppressed by the
16 antipsychotic drugs. But I don't know any way to
17 test or prove that, but there's a certain
18 plausibility to it.

19 Thinking further, what about the patient
20 care process? It may be, particularly with
21 demented patients, that squeaky wheels get more
22 attention and better supportive care. And it may

1 be that chemical or other restraints, which is
2 basically how these drugs are being used,
3 facilitate neglect. We like to think that all our
4 patients get good care, but it's sort of like
5 woebegone, all the kids are above average.

6 Remember, these are clinical trials, and in
7 clinical trials, people tend to get a little closer
8 attention. And these are people who are concerned
9 about, in this case, maybe their loved ones'
10 medical condition. They want them to get better.
11 They're in the trial to see if they can get better,
12 and yet maybe this neglect may still be happening.

13 But again, it's purely speculative. I don't
14 have any direct evidence whatsoever. And I don't
15 know even if this were true, how it might be
16 interpreted in terms of how you might deal with
17 people with Parkinson's disease who are in slightly
18 different situations.

19 So that's my summary, and I'll answer any
20 questions.

21 **Clarifying Questions to FDA**

22 DR. BRENT: David Brent. You indexed the

1 death rate in this drug versus all the other trials
2 in people with dementia, but my understanding is
3 that not everybody who came into the trial with
4 Parkinson's disease psychosis was demented. And
5 kind of a related question is that it looked like
6 the effect was stronger, the beneficial effect was
7 stronger in people who had evidence of dementia.

8 So I'm just wondering, either in your
9 analyses or the sponsor's, whether people took out
10 those -- just looked at those with dementia and see
11 what the ratio of benefit to harm was.

12 DR. STONE: Well, I didn't look specifically
13 at pimavanserin for that issue, but that's true.
14 And that's one of the differences that you can take
15 with as many grains of salt as you think is
16 appropriate. But maybe Paul or someone from Acadia
17 might want to comment on that.

18 DR. STANKOVIC: We did do analysis by
19 looking separately at the patients that had mild
20 dementia. They were 24 to 21 on the Mini-Mental
21 Status Exam. There was a smaller group of those
22 patients, about 50 of those patients, and then they

1 appeared to have a somewhat better effect.

2 Slide up. So these are on the left side the
3 patients between 21 and lower than 25 on dementia.
4 Again, a little bit of caution in interpretation
5 considering that only 50 patients were in that
6 group.

7 DR. BRENT: I was just curious, do you know
8 about the serious adverse events in that group?

9 DR. STANKOVIC: Yes. Slide up. So this is
10 distribution of adverse events, serious adverse
11 events, adverse events resulting in death, and
12 adverse events leading to discontinuations. On the
13 left side are those that are 21 to 25, and on the
14 right side are those that did not have, according
15 to Mini-Mental Status Exam, dementia.

16 So we didn't see dramatic differences in
17 that particular population in any of the events
18 that we are talking now.

19 DR. BRENT: Thank you.

20 Dr. Schmid?

21 DR. SCHMID: Just following up on that then,
22 it looks like there's more efficacy in those who

1 have less serious baselines, but there's more
2 adverse events in those who have more serious
3 baselines, if I read that slide correctly.

4 DR. STANKOVIC: In terms of efficacy, we
5 separate in both groups, but it does appear again,
6 considering the smaller number of patients, that
7 the effect size is larger.

8 Slide up. In terms of your --

9 DR. SCHMID: So looking here at the greater
10 than 25, you have 12 serious events versus 5,
11 right?

12 DR. STANKOVIC: Right.

13 DR. SCHMID: But the efficacy was much less
14 in that group.

15 DR. STANKOVIC: Right.

16 DR. SCHMID: So therefore, it would seem
17 like in that group, you're not getting much
18 benefit. The cost-benefit -- the harm-benefit
19 ratio is much worse than in the other group.

20 DR. BRENT: Smaller is worse.

21 DR. SCHMID: Yes, exactly. What I'm saying
22 is there's more efficacy in the less than 25, but

1 there's more serious events in the greater than 25.
2 Therefore, the cost-benefit is very different in
3 those two groups.

4 DR. STANKOVIC: Right.

5 DR. BRENT: Dr. Grieger?

6 DR. GRIEGER: Are there any reasonably
7 controlled trials that actually look at a hazard
8 ratio of death within six months of starting these
9 drugs? I was just reviewing a naturalistic one
10 that I found this morning, but there are all kinds
11 of factors on why somebody gets put on an
12 antipsychotic.

13 Is there anything that's been controlled in
14 nature, same degree of symptomatology, patient A or
15 group A gets treated with risperidone, group B is
16 left untreated, and who dies?

17 DR. STONE: I think that's exactly what
18 these studies do. I mean, you've got the
19 randomized controlled trials. I don't have the
20 hazard ratio because we didn't have individualized
21 data, but we did have degree of exposure, length of
22 exposure. So these studies did vary significantly

1 in their lengths. So in order to control for that,
2 we did length of exposure.

3 So under these circumstances, the hazard
4 ratio should be very similar to what we saw here
5 for the mortality incidence ratio. So it's
6 70 percent higher, I think, when you look at it.

7 DR. GRIEGER: Okay.

8 DR. BRENT: Dr. Duda?

9 DR. DUDA: Were you asking, Dr. Grieger,
10 that in PD because there's --

11 DR. GRIEGER: That's a good question because
12 we just heard a talk that talked about a lot of
13 dementia, which not everybody with PD -- most
14 people -- well, I don't know. Not everybody with
15 Parkinson's disease has dementia. So I don't know
16 how they're comparable for a Parkinson's population
17 other than naturalistic studies that are done
18 through the VA and places like that.

19 DR. DUDA: Yes, right. I think they're
20 different.

21 DR. BRENT: Okay. Thank you, everybody, for
22 your participation. We're now going to break for

1 lunch, and we'll reconvene at 1:00 o'clock. Take
2 any of your personal belongings, and we just remind
3 ourselves that we should have no discussion about
4 these topics.

5 (Whereupon, at 12:05 p.m., a lunch recess
6 was taken.)

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A F T E R N O O N S E S S I O N

(1:01 p.m.)

Open Public Hearing

DR. BRENT: Good afternoon. 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, the FDA believes that it is important to understand the context of an individual's presentation.

For this reason, the FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the committee of any financial relationship that you may have with the sponsor, its product, or if known, its direct competitors.

For example, this financial information may include the sponsor's payment of your travel, lodging, or other expenses in connection with your attendance at this meeting.

Likewise, the FDA encourages you at the beginning of your statement to advise the committee

1 if you do not have any such financial
2 relationships. If you choose not to address this
3 issue of financial relationships at the beginning
4 of your statement, it will not preclude you from
5 speaking.

6 The FDA and this committee place importance
7 in the open public hearing process. The insights
8 and comments provided can help the agency and this
9 committee in their consideration of the issues
10 before them. That said, in many instances and for
11 many topics, there will be a variety of opinions.

12 One of our goals today is that for this open
13 public hearing to be conducted in a fair and open
14 way where every participant is listened to
15 carefully and treated with dignity, courtesy and
16 respect. Therefore, speak only when recognized by
17 the chairperson. Thank you for your cooperation.

18 Will speaker number 1 step up to the podium
19 and introduce yourself? Please state your name and
20 any organization you are representing for the
21 record.

22 DR. SCHMIDT: My name is Peter Schmidt. I

1 am the chief mission officer for the National
2 Parkinson Foundation. My lodging here today was
3 paid for by the sponsor, and NPF has received
4 several grants from Acadia. I personally have not
5 received anything from the sponsor.

6 I think that the group has addressed very
7 effectively the drug in question and its efficacy
8 and the need for it. I'd like to talk a little bit
9 about the need for a drug in this space in
10 particular.

11 When I started at NPF, one of the first
12 initiatives we launched was something called the
13 Aware and Care Program, which was a kit for
14 patients who are hospitalized to help them with
15 advocating for their own best care.

16 We did some research as a preliminary to
17 launching this, and one of the things that we
18 found, as we reviewed the literature and as we
19 conducted interviews with patients, was that there
20 was a common story that we were hearing from
21 patients in our community. And that was that a
22 patient would be admitted to the hospital with a

1 relatively mild complaint, have their medication
2 schedule changed or be taken off medications,
3 develop what was told to the patient or the family
4 was confusion, be put on an antipsychotic, and the
5 patient would die.

6 We heard many cases. I have many documented
7 cases of families coming to us and telling us that
8 a patient hospitalized for constipation or for some
9 other relatively mild complaint would develop
10 confusion and be put on a dopamine-blocking
11 antipsychotic, and would die.

12 This has been something that -- so when we
13 developed the kit, we put very explicit
14 instructions that we put together working with
15 physicians from our centers of excellence about how
16 to talk to hospital staff about antipsychotics.

17 When we first were made aware of
18 pimavanserin, my first question was, well, do we
19 have data that shows that we really need a new
20 antipsychotic medication? And I went into -- I
21 serve as the PI on a large observational study of
22 Parkinson's patients called the Parkinson's

1 Outcomes Project. It's been going on for about
2 seven years now. It's got 8,000 patients in the
3 database.

4 I took this group of patients, and I said,
5 "Let's look at patients who develop psychosis in
6 the third year and how they were doing in the
7 previous two years." And we found that for several
8 years prior to being treated for psychosis, they
9 were experiencing really significant detriments to
10 their quality of life, three times the minimally
11 significant change on average -- a clinically
12 significant change on average on the PDQ-39.

13 So we feel like there really is a need for
14 better antipsychotic care. And my time is up so I
15 will step down.

16 DR. BRENT: Thank you.

17 Will speaker number 2 step up to the podium
18 and introduce yourself? Please state your name and
19 any organization you are representing for the
20 record.

21 MS. CASAVANT: Good afternoon. Thank you
22 for this opportunity to speak with you today. My

1 name is Elaine Casavant. I'm a registered nurse,
2 and I work with Parkinson's Disease Foundation on
3 the People with Parkinson's Advisory Council.

4 I myself am a caregiver and wife of a
5 patient who was diagnosed in 1991 after almost
6 eight years of symptoms that were clearly
7 Parkinson's. He was 46 at the time. We went to
8 the neurologist. He was put on Sinemet and
9 Eldepryl, and had a 10-year plateau of good health,
10 exercise, and enjoyed himself. He was still
11 working. This ended in 2002. Eldepryl was decided
12 not to be effective, and he was placed on one
13 adjunct after another, each problematic, and
14 behavioral issues were terrible.

15 In 2008, he went through an evaluation, had
16 DBS done in 2009. And again, we had a nice plateau
17 until about 2011. There came a turning point in
18 the disease. He had a cognition, perception,
19 hallucinations, delusions, paranoia, increased
20 insomnia, anxiety, hostility. And these things
21 would vary in severity day to day and would worsen
22 and have continued to worsen over time.

1 We've used every drug for sleep, anxiety,
2 and all of these symptoms, and some of them have
3 been more problematic than the symptom itself, and
4 none of them have worked very well.

5 I'm a private person, and I'm just going to
6 give you a quick example. My husband, ever the
7 engineer, woke up in the night screaming and
8 hollering about children in his room. Put the
9 lights on, got him quieted down, convinced him
10 there were no children. He went back to sleep, and
11 an hour later, he was screaming again.

12 I trotted down the hall and tripped over
13 wire he had strung across the door casing to keep
14 the children out. This is typical. It goes on
15 half a dozen times a day. We need something to
16 help with this.

17 I am an administrator for online groups of
18 caregivers who train and then go out and start
19 caregiver groups and support groups. And surveys
20 that we did showed that this is the single biggest
21 impediment to home care. We can deal with all the
22 symptoms of Parkinson's, but this is the issue that

1 will put him in a nursing home. And I would like
2 to be able to have a drug that might possibly give
3 him quality of life and a return to some normalcy.

4 Thank you for your time.

5 DR. BRENT: Thank you.

6 Will speaker number 3 step up to the podium
7 and introduce yourself? Please state your name and
8 any organization you are representing for the
9 record.

10 MS. CONWAY: Good afternoon. My name is
11 Mary Ann Conway. Acadia has paid for my travel and
12 lodging.

13 PDP has deeply affected my family for
14 generations. In 1985, I moved to Detroit for a
15 job, and my father called me every day. As time
16 went on, his robust voice turned weak and
17 melancholy. There was something wrong, so after a
18 year, I moved back home.

19 When I hugged my father, he'd lost so much
20 weight, I thought he'd break. Once a wonderful
21 dancer, he couldn't walk. He shuffled. I heard
22 the word "Parkinson's" after his body seemed to

1 freeze in place and he'd fall over.

2 My dad helped our country reach great
3 heights as a control panel production manager for
4 Gemini, Mercury, and Apollo, but my heart sank the
5 day I walked into the kitchen and he introduced me
6 to a coworker. I looked to see where he was
7 pointing. It was an empty chair. He died in 1989.

8 In 2014, my sister Judy was diagnosed with
9 Parkinson's. She remembered his physical changes.
10 I remembered mental changes. I was shocked when
11 she said there was dignity in jumping off the
12 George Washington bridge, and if I love her, I'd
13 let her go. She was that depressed and frightened.

14 I love Judy. I'm not letting her go, and
15 that's why I'm here today. Judy was an English
16 teacher and social worker with many interests. But
17 these days, only moments pass before Judy sees
18 snakes on her hands, men in the trees, babies
19 upstairs, dogs at the door, barbershop quartets in
20 walls. She ran out of the house after a car,
21 seeing her daughter in the front seat.

22 It's dangerous and distressing. She can't

1 spend time with her grandchildren because of this
2 altered state of reality.

3 I was dismayed to learn after 30 years not
4 much has changed in the treatment of PDP.
5 Klonopin, Seroquel, Clozaril, Zyprexa were
6 administered and did not relieve her
7 hallucinations, just seemed to worsen Parkinson's
8 symptoms and motor abilities.

9 Stiffness increased, and Judy became
10 zombie-like. She could not walk unaided as she
11 faltered and fell. She could not get up, down, sit
12 on the toilet, dress, feed, or groom herself. She
13 became a totally different person, sobbing,
14 speaking unintelligible phrases, verbally abusing
15 her husband of 50 years.

16 Because of the horrible side effects, Judy
17 was taken off all antipsychotics. The stress and
18 demands of the disease and unavailability of any
19 effective drug has thrown the family into chaos.
20 I'm especially concerned for the health of her
21 husband.

22 Judy told her psychiatrist all she wants is

1 some normalcy back. The doctor conceded they've
2 tried everything and there's nothing left. I
3 watched as Judy and her husband sat hopeless.

4 With the approval of pimavanserin, there
5 would be hope, a vast improvement in Judy's daily
6 life, allowing Judy to play and talk with her
7 grandchildren again. My daughter had one chance to
8 sit on her grandfather's lap in 1989. I keep that
9 empty chair as a memory of that day.

10 You have the chance to bring hope to Judy,
11 our family, hope that we give her grandchildren
12 real memories instead of an empty chair. I'm here
13 today to ask that you recommend the approval of
14 pimavanserin for my sister and so many others
15 affected by hallucinations brought on by
16 Parkinson's disease. Thank you very much.

17 DR. BRENT: Thank you.

18 Will speaker number 4 step up to the podium
19 and introduce yourself? Please state your name and
20 any organization you're representing for the
21 record.

22 MR. THOMPSON: Hi. My name is Ted Thompson.

1 I'm president and CEO of the Parkinson's Action
2 Network. Because Dr. David Kreitzman couldn't be
3 here today, I'm standing in for him while you watch
4 the video that he provided.

5 (Videoplayed and transcribed.)

6 DR. KREITZMAN: Hi. I'm Dr. David
7 Kreitzman, a board certified neurologist, movement
8 disorder specialist, who is submitting this video
9 in regards to your application and acceptance of
10 Nuplazid for approval for Parkinson's disease
11 psychosis.

12 As you know, this is a tremendous unmet need
13 for patients with Parkinson's disease, and we have
14 no current available tools to treat directly these
15 symptoms associated with the disorder.

16 I'm a primary investigator who worked for
17 Acadia in the relevant program for pimavanserin,
18 the parent drug, and Nuplazid, and also work as a
19 consult for the company in developing marketing
20 strategies for potential product approval. But I
21 thought my best service to you would be to describe
22 two patients that I enrolled in the trial and the

1 benefits that they received being on Nuplazid.

2 The first patient was a patient who
3 experienced visual hallucinations. Here's a
4 patient that often was falling going to the
5 bathroom or urinating in his bed. That was what
6 the presenting symptoms were.

7 When asked why he was falling while going to
8 the bathroom, he said he was trying to tiptoe
9 around the dogs that were very vicious and would
10 wake up and bark. So when I tried to explain to
11 the spouse that the dogs should probably be moved
12 from the bedroom, it was then that it was
13 discovered that there were no dogs in the bedroom.
14 They were visual hallucinations.

15 She was also very concerned because he was
16 urinating in the bed quite often, and it became
17 very cumbersome to her and overwhelming that she
18 had to constantly change the sheets and/or take him
19 to the emergency room every time he fell and would
20 fall and bruise himself in the doorway of the
21 bathroom.

22 Since being on the medication, actually in

1 the open-label portion of the trial, those dogs
2 basically went away, and he stopped falling going
3 to the bathroom and has stopped urinating in the
4 bed. This is obviously an improvement for him,
5 both reducing his risk of injury and falls, and
6 also greatly improved their relationship because
7 there was less work for her to do -- one less thing
8 for her to do when managing his symptoms of
9 Parkinson's disease.

10 The second such patient was a patient who
11 had delusions of spousal infidelity who thought her
12 spouse was cheating on her by playing music
13 upstairs in the bedroom on the second floor,
14 literally playing music, although the patient does
15 not play an instrument -- the spouse actually does
16 not play an instrument; or she often heard them
17 having conversations in closets. She would often
18 run up and down stairs, putting herself at risk for
19 falling, and would often run into closets thinking
20 she was going to catch him speaking in the closet.

21 Since being in the program, these delusions
22 actually reduced significantly, where they were not

1 bothering her [indiscernible]. From her side of
2 the story, it would happen once in a while, but she
3 knew they were not real. So for her and for he,
4 this was a great improvement in their dynamic as a
5 family and reduced her risk by running up and down
6 stairs.

7 I hope these were helpful examples. These
8 are what we see every day in clinical practice when
9 we identify patients with Parkinson's disease
10 psychosis and why the necessity of a tool such as
11 Nuplazid would be very effective and helpful for
12 us. Thank you for your consideration.

13 DR. BRENT: Thank you.

14 Will speaker number 5 step up to the podium
15 and introduce yourself? Please state your name and
16 any organization you're representing for the
17 record.

18 MS. PEREZ: My name is Brittmarie Janson
19 Perez. My accent is Swedish and Spanish. A
20 retired anthropologist, I'm the widow of Frank
21 Perez who was afflicted by Parkinson's disease
22 psychosis in the last year of his life and did not

1 get pimavanserin.

2 I'm here today because when his doctors
3 could find no medication to allay his terrifying
4 hallucinations, having read about pimavanserin, I
5 contacted Acadia directly and kept in touch.
6 Acadia paid for my travel and lodging, but I have
7 no financial relationship with the company.

8 My testimony is based on the daily log I
9 kept of my husband's condition. Frank was a calm,
10 strong and supportive man, the kind of person who
11 brings out the best in you. We had been happily
12 married for 40 years when Parkinson's psychosis
13 changed him.

14 Parkinson's psychosis can be diabolic. The
15 devilishly detailed hallucinations, which haunted
16 Frank stimulated maximum paranoia, preyed not only
17 on his known fears of heights and snakes but also
18 provoking feelings of vulnerability, abandonment
19 and betrayal that he had never manifested before,
20 that he was besieged by gangsters, that he was lost
21 and could not find his way home, that I was having
22 an affair and divorcing him with the approval of

1 our daughters, and that I had died.

2 When Frank needed round-the-clock care, I
3 was able to keep him at home by hiring three
4 excellent caregivers at a cost of \$4,000 monthly.
5 But finally, we could not control him. A man who
6 should have died in his home surrounded by his
7 loved ones spent the last three weeks of his life
8 in the dementia ward of a nursing home. He died
9 alone at 1:00 o'clock in the morning on the 1st of
10 December 2014.

11 Financially, the cost of Parkinson's disease
12 psychosis is high. For the victims, the
13 psychological suffering is excruciating. Their
14 families' emotional trauma does not end with their
15 loved one's life. Our memories are scarred
16 forever.

17 For the sake of the thousands afflicted by
18 Parkinson's disease psychosis whose agony may be
19 averted or diminished by pimavanserin, I urge you
20 to recommend its approval. Thank you.

21 DR. BRENT: Thank you.

22 Will speaker number 6 please step up to the

1 podium and introduce yourself? Please state your
2 name and any organization you're representing for
3 the record.

4 DR. EBERLING: Good afternoon. My name is
5 Jamie Eberling. I'm a scientist from the Michael
6 J. Fox Foundation. I have no financial
7 relationship with Acadia, nor do I stand to gain
8 financially should pimavanserin be approved by the
9 FDA, although Acadia did pay for my travel today.

10 People think Parkinson's disease and see a
11 tremor or some shuffling with slow movements and
12 impaired gait. Those motor symptoms are the
13 cardinal features of Parkinson's, but they are far
14 from all that the 1 million Americans with this
15 disease experience. We have gotten pretty good at
16 treating these motor symptoms. However, there are
17 a number of non-motor symptoms that go largely
18 untreated.

19 Estimates vary, but meta-analyses have shown
20 that more than 50 percent of people with
21 Parkinson's disease may experience what we call
22 Parkinson's disease psychosis. Patients may

1 experience hallucinations, delusions, illusions, or
2 false sense of presence. Parkinson's disease
3 psychosis and its effects are debilitating, costly,
4 both emotionally and financially.

5 Unfortunately, we are not able to treat
6 Parkinson's disease psychosis well. First,
7 clinicians rule out conditions other than
8 Parkinson's disease that may be causing temporary
9 psychosis such as infection or dehydration. It is
10 also possible that the medication used to treat
11 some Parkinson's symptoms such as dopamine agonist
12 for tremor and rigidity are causing psychosis.
13 Lowering the dose of the agonist may help, but this
14 may exacerbate the motor symptoms.

15 The doctor may prescribe antipsychotics to
16 prevent the hallucinations or delusions, but there
17 lies another trade-off. Available antipsychotics
18 block dopamine receptors, and thereby the effect of
19 medication for motor symptoms. Currently treating
20 Parkinson's disease psychosis requires a choice, an
21 ultimatum, either motor or mind.

22 A new option arises with pimavanserin.

1 Trials have shown that blocking only serotonin
2 receptors can ease psychosis without interfering
3 with dopamine therapies and worsening motor
4 symptoms. The benefit this could bring to the
5 individual would be significant. Psychosis is
6 disruptive to one's day, to one's identity, and to
7 one's sense of safety. The Parkinson's community,
8 patients and loved ones as well would benefit.

9 I've been involved in Parkinson's research
10 for over 20 years. At the Fox Foundation, I help
11 to review over a thousand research proposals per
12 year for projects aimed at developing new therapies
13 for Parkinson's disease. We have a broad view of
14 the therapeutic landscape, and in my opinion,
15 Parkinson's disease psychosis is a major unmet need
16 with few largely ineffective treatment options.

17 The impact of a treatment for Parkinson's
18 disease psychosis would be profound both for
19 patients and their loved ones and would improve the
20 lives of many living with this disease today and
21 the more who will come until we find a cure for
22 Parkinson's. Thank you for your attention.

1 DR. BRENT: Thank you.

2 Will speaker number 7 please step up to the
3 podium and introduce yourself? Please state your
4 name and organization you're representing for the
5 record.

6 DR. FOX-RAWLINGS: Thank you for the
7 opportunity to speak today. My name is
8 Dr. Stephanie Fox-Rawlings. I was previously a
9 neuroscientist at the Children's National Medical
10 Center, and I'm now a senior fellow at the National
11 Center for Health Research.

12 Our research center analyzes scientific and
13 medical data to provide objective health
14 information to patients, providers, and
15 policymakers. We do not accept funding from the
16 drug or medical device industry. I have no
17 conflicts of interest.

18 We strongly support the efforts to find safe
19 and effective treatments for patients with
20 Parkinson's disease so that patients can live as
21 independently as possible. Reducing psychotic
22 symptoms is very important, but not when the risk

1 of harm outweighs the potential benefit. We
2 understand that psychotic symptoms are upsetting
3 and debilitating. The question is, if a drug needs
4 to be taken for the rest of one's life and the drug
5 can shorten one's life, then how much benefit is
6 required for FDA approval?

7 The data presented today show that
8 pimavanserin provides a statistical improvement in
9 symptoms. However, the average improvement of
10 3 points or 23 percent on the SAPS-PD scale does
11 not appear to be clinically meaningful.

12 It is also concerning that the SAPS-PD scale
13 may not test the appropriate types of
14 hallucinations and delusions. Since the scale was
15 the shortened version of the scale for
16 schizophrenia, it focuses on the types of
17 hallucinations and delusions that are prevalent
18 with schizophrenia, but these are not the most
19 common with PDP.

20 The scale may give undue weight to less
21 common hallucinations like auditory hallucinations,
22 and it does not include related symptoms such as

1 illusions.

2 If the drug produces modest benefits with
3 few side effects, it still can be very useful to
4 patients. However, during the 6-week trials,
5 approximately 10 percent of patients taking the
6 drug had a severe adverse event, about twice that
7 of patients taking placebo. This included three
8 patients who died taking the 34-milligram dose as
9 opposed to one taking placebo.

10 Other adverse events included psychiatric
11 and nervous system disorders, suicidal thoughts,
12 and confusion. Furthermore, patients are expected
13 to be treated for years. Without longer
14 placebo-controlled studies, we cannot predict
15 whether the treatment will provide long-term
16 benefit or if long-term exposure will affect the
17 rate of serious adverse events.

18 The pivotal study cannot address these
19 questions. The sponsors did provide data for a
20 long-term, open-label study, but we cannot
21 determine its relevance without a comparison group.

22 Another issue is that the drug does not

1 statistically improve psychotic symptoms for
2 non-whites, females, or patients under the age of
3 65 or over 75 years old. However, small numbers
4 for these groups can make this data difficult to
5 interpret.

6 The drug may be beneficial for a
7 subpopulation of patients with PDP, perhaps with
8 specific types of psychosis or within an age range.
9 However, the current data does not provide enough
10 information to determine if the benefits greatly
11 outweigh the risks for any subgroup.

12 In conclusion, because of the concerns over
13 limited efficacy, the tests used, and the high
14 incidence of adverse events, we cannot urge you to
15 support the approval of pimavanserin. Thank you
16 for your time and consideration of our views.

17 DR. BRENT: Thank you.

18 Will speaker number 8 please step up to the
19 podium and introduce yourself? Please state your
20 name and any organization you're representing for
21 the record.

22 MR. THOMPSON: Good afternoon. My name is

1 Ted Thompson, president and CEO of the Parkinson's
2 Action Network. In terms of our financial
3 interest, Acadia did provide local ground
4 transportation for me today, and we have received
5 grants for them for our annual Udall awards dinner
6 and our annual PAN forum. But no benefit would
7 come to us whether this drug is approved or not.

8 Parkinson's Action Network is a unified
9 voice of the Parkinson's community working on
10 public policy issues. We support an efficient
11 clinical trial regulatory framework that protects
12 patients, maximizes limited resources, and
13 considers the full burden of Parkinson's disease.

14 We do not endorse specific diagnostic
15 products, drugs or therapies, but we are keenly
16 interested in all reasonable ways to expand the
17 number of tools available in our very limited
18 arsenal against Parkinson's.

19 I'm pleased to stand before you today to
20 speak briefly about the critical unmet need of
21 Parkinson's disease psychosis. PD is often
22 characterized as a movement disorder, but the

1 realities of the patient experience demonstrate a
2 prevalence of debilitating non-motor symptoms.
3 Such symptoms are equally, if not more challenging,
4 to quality of life as the motor symptoms are.

5 PDP is a non-motor symptom without targeted
6 treatment options. Studies suggest that up to
7 50 percent of people with Parkinson's disease are
8 expected to develop psychosis as their disease
9 progresses. Parkinson's disease psychosis can
10 include hallucinations and delusions that worsen in
11 frequency and intensity over time.

12 The symptom can contribute to an increased
13 risk of hospitalization and institutionalization
14 and can significantly impair the quality of life
15 for patients and their caregivers. PDP can become
16 taxing to the extent where patients require
17 long-term care, and for the greater duration, an
18 average of nearly 100 days longer than those who do
19 not exhibit psychosis symptoms.

20 Currently, management of PDP is quite
21 limited. In an effort to control the symptoms of
22 the disease, doctors may first consider reducing

1 medications used to control the motor symptoms
2 and/or prescribe antipsychotics, which can
3 interfere with motor control. These antipsychotics
4 have not been approved, nor have they been proven
5 effective in treating Parkinson's disease
6 psychosis.

7 Either approach is less than optimal because
8 of the negative impact on motor symptom control and
9 quality of life for the patient. As a result,
10 there's a significant gap in treatment for PDP and
11 what is needed to manage the symptom without
12 potentially worsening the other aspects of the
13 disease.

14 The PD community applauds the FDA's
15 commitment to development and approval of drugs
16 that address serious unmet needs. We believe
17 Parkinson's disease psychosis falls into that
18 category, and again, not only does that therapy
19 hold great promise for the patient, it can
20 dramatically improve the lives of the caregivers
21 and all those around the patient who is suffering
22 from Parkinson's disease psychosis.

1 Thank you very much.

2 DR. BRENT: Thank you.

3 Will speaker number 9 step up to the podium
4 and introduce yourself? Please state your name and
5 any organization you're representing for the
6 record.

7 MR. THOMPSON: Sorry. I should have just
8 stayed up here. Again, I'm Ted Thompson, president
9 and CEO of the Parkinson's Action Network. Because
10 Francis Philibert could not be here, I'm standing
11 in for him as you view the video.

12 (Video played and transcribed.)

13 MR. PHILIBERT: My name is Francis Philibert
14 from Prospect, Connecticut, and this is my wife
15 Jackie. She's been diagnosed with Parkinson's for
16 over 33 years. And we started this clinical trial
17 in 2004, and we've been on it for 11 years.

18 To get on the clinical trials, we were
19 approved by Dr. Murphy who had listened to some of
20 the comments that I made, what she was doing such
21 as accusing myself of having affairs, believing it,
22 and so forth.

1 Also, her hallucination that she was having
2 outside one day, where she was outside and there
3 was a tree we have next to the house. She started
4 yelling, and I had to run out there because I
5 thought she had gotten hurt. But no, it was a boy
6 that was in the tree, and in this tree, it was all
7 covered with bees. Of course, there were no bees
8 there or anything like that. So I just played
9 along, and then she was okay. And she came in.

10 These are the things that I brought up to
11 Dr. Murphy. And Dr. Murphy thought that we were
12 probably just right for this trial. So we got into
13 the trial. And during the trial, I did find some
14 improvements because she was also accusing me of
15 having an affair. And I found after a while that
16 she was no longer mentioning it. And as time went
17 on, I noticed she was kind of mellow. There was
18 hardly any anxiety. So right now, she's still
19 currently on the two pills.

20 About a month and a half ago, I found what
21 this trial is all about because before then, didn't
22 know; and found out everything that I had just said

1 to you about hallucinations, delusions, all of
2 those things had been kind of diminished.

3 Yes, there were times in the beginning, it
4 was very tough, but this is what I feel after
5 having this clinical trial, that I believe it does
6 work. And I believe that if it does work on what
7 it says it does, which I feel that it did with my
8 wife, that it would help an awful lot of caretakers
9 besides the patient.

10 So I ask again to approve this, to grant the
11 [indiscernible] so that people's lives, they can
12 have a better quality of life. This is what I find
13 that I have here, a better quality of life. I
14 actually beg you because I really believe in this
15 product. I thank you for listening to me.

16 DR. BRENT: Thank you.

17 Will speaker number 10 please step up to the
18 podium and introduce yourself? Please state your
19 name and any organization you're representing for
20 the record.

21 DR. HERMANOWICZ: My name is Neal
22 Hermanowicz. I'm a movement disorders neurologist

1 at the University of California Irvine where I
2 treat people with Parkinson's disease. And I have
3 served as an investigator for trials in
4 pimavanserin, and I have also served as a
5 consultant to Acadia.

6 I am the person in my clinic who makes the
7 diagnosis of Parkinson's disease-related psychosis,
8 and I initiate treatment plans for my patients.
9 I've included some case examples from my practice
10 because I think they're not outliers, but I thought
11 they would be illustrative.

12 For example, one of my patients who's in his
13 early 70s awakened his wife recently at about 1:00
14 in the morning. He was in the garage and had
15 deliberately set off the car alarm to summon help,
16 feeling that he was being pursued by intruders who
17 were in his home intending to do him harm. The
18 following day, he asked his wife, "Are you trying
19 to kill me?"

20 After discussion with his general
21 neurologist within the Kaiser Permanente system, he
22 was initiated on quetiapine. And clozapine

1 apparently within that system is restricted to some
2 psychiatrists. And in my last follow-up with him,
3 I'm not yet confident that his psychosis symptoms
4 are yet controlled.

5 Another woman in my practice, 80 years old,
6 has been my patient for 10 years or more, has had
7 auditory hallucinations, which have been very
8 troubling. She hears her deceased son calling her
9 name asking for help. She's also been hearing
10 conversations she believes that her husband is
11 having with a girlfriend that he has hidden
12 elsewhere in their home.

13 Her husband spends his days bathing her and
14 dressing her and feeding her, and now spends
15 additional time going to the pharmacy once a week
16 for clozapine and also arranging for the blood test
17 for his wife. The drug has been helpful, but it's
18 added significantly to his daily burden.

19 The last example is another patient of mine
20 in the past who was experiencing hallucinations and
21 some confusion about his wife's identity. I did
22 reduce his Parkinson's medications and discussed

1 treatment options with the patient and his wife,
2 including quetiapine and clozapine, touching upon
3 efficacy, possible side effects, blood tests that
4 are required for clozapine. And after this
5 discussion, the wife declined the interventions and
6 elected to simply observe the symptoms.

7 Her husband was later removed from his home
8 by the police, summoned by his wife after he
9 assaulted her in the kitchen of their home under
10 the belief that she was not his wife and was there
11 to do him harm.

12 The need for additional therapy for
13 Parkinson's disease psychosis is certainly evident
14 to my patients and their family members. It's
15 evident to me in my daily work, and I hope
16 pimavanserin will be available to me to provide to
17 my patients. Thank you for your attention.

18 DR. BRENT: Thank you.

19 Will speaker number 11 step up to the podium
20 and introduce yourself? Please state your name and
21 any organization you're representing for the
22 record.

1 MS. WADE: Good afternoon. My name is Zoey
2 Wade, and I'm from Northport, Long Island, New
3 York. I have no financial relationship with
4 Acadia.

5 I asked to speak about my grandmother's
6 experience with Parkinson's disease psychosis
7 because it affected our entire family, me in
8 particular. My grandmother and I have been very
9 close my entire life. We've always spent a lot of
10 time together, from the time I was young, memories
11 of babysitting, sleepovers, baking homemade pumpkin
12 pie, and so much more.

13 The entire family was upset when my grandpa
14 was diagnosed with Parkinson's disease. We worried
15 about how she would cope with the motor symptoms,
16 but the reality is that my grandpa's hallucinations
17 and delusions are much more challenging to deal
18 with than her reduced mobility.

19 The hallucinations and delusions made her
20 agitated and nervous. I'd see her constantly
21 peering out the window to check whether there were
22 people in the backyard who might be staring into

1 the house. In the morning, she'd regularly see a
2 group of adults who weren't actually there doing
3 Tai Chi in the backyard. The idea of strangers in
4 her yard and near her home upset her so much that I
5 often would spend the night in her home to reassure
6 her that she was safe.

7 It was very upsetting to realize that some
8 of my grandmother's delusions were directly
9 associated with me. She worried and believed that
10 I was in danger when I wasn't at her house, or
11 sometimes she thought she would see me in the room
12 even when I wasn't there, and then get upset when I
13 wouldn't respond to her when she spoke to me. It
14 really hurt me that I couldn't help her understand
15 what was real and what was not.

16 When my grandmother enrolled in the clinical
17 trial for Nuplazid, we didn't know what to expect
18 or even if she was on the drug, but we soon
19 realized that she must be taking the drug because
20 she really returned to herself. Her hallucinations
21 reduced, and she better understood what was real
22 and what was imaginary.

1 I was so happy that she seemed like her old
2 self. Her memory and humor are incredible, and I
3 am so grateful to be able to talk with her and
4 spend quality time with her again. She's able to
5 live in her own home and keep her dignity intact.
6 This drug has given my grandma both quantity and
7 quality of life.

8 I hope the panel today will recommend
9 Nuplazid for approval. It's made such a difference
10 in my grandmother. My grandma needs this
11 medication. I know other families, patients would
12 benefit from having this treatment to try. Thank
13 you.

14 DR. BRENT: Thank you.

15 Will speaker number 12 step up to the podium
16 and introduce yourself? Please state your name and
17 any organization you're representing for the
18 record.

19 MS. WADE: My name is Jody Wade. I'm from
20 Northport, Long Island, New York. I have no
21 financial relationship with Acadia and will not
22 gain financially should pimavanserin be approved.

1 I'm the youngest daughter of Ruth Ketcham,
2 who asked me to speak on her behalf. My mom was
3 diagnosed with Parkinson's disease and later
4 Parkinson's disease psychosis about eight years
5 ago. My mother is not demented, but she
6 experienced hallucinations and delusions multiple
7 times every single night.

8 In the beginning, the hallucinations were
9 not necessarily frightening or distressful, but
10 they did become so. My mother believed that people
11 were in her house and watching her throughout the
12 night. It impacted her life, that she no longer
13 would wear nightgowns to sleep in and switched to
14 pajamas so that she would be covered and the people
15 wouldn't see her when she got out of bed.

16 Coat racks became frightening because she
17 thought that's where the people were hiding. She
18 believed that there were animals in her house at
19 night and we needed to call an exterminator. One
20 night she became so fearful, she believed somebody
21 was outside her back window when she was sleeping.
22 She called 911. She was very frightened and call

1 us in the middle of the night to say that somebody
2 was outside her home. She was just terrified.

3 This affected me greatly in that I'm a nurse
4 and I just couldn't help her. It was
5 heartbreaking. I could fix so many of the
6 problems, the motor problems of Parkinson's, but I
7 could not stop the hallucinations or convince her
8 otherwise. There is no one in the world I would
9 want to help more than my mom, and I was afraid
10 that this was going to be the remainder of her
11 life.

12 My mom started the drug trial because she
13 realized she could potentially help others. It
14 didn't take long before I knew that she was
15 receiving the real medication. I was sure because
16 the hallucinations had stopped completely.

17 If my mom had not enrolled in this trial,
18 she would have not been able to remain in her own
19 home. We would have had no choice but to place her
20 in a nursing home, which we absolutely do not want
21 to do.

22 The medication enabled her to sleep through

1 the night, feel safe and secure in her house, and
2 return to her previous state. She was now well
3 rested. She enjoyed going out and was able to do
4 the things she had done before. Since her motor
5 skills were somewhat intact, without the
6 debilitating hallucinations, she was given years of
7 her freedom back.

8 Fast forward to today, my mom still lives in
9 her own home, recently celebrated her 92nd
10 birthday, and remains an avid Met fan and can give
11 accurate recaps of every game. So that's our
12 story, and that's why I'm asking you to grant the
13 FDA approval for this medication that's been so
14 very helpful for my mother. Thank you.

15 DR. BRENT: Thank you.

16 Will speaker number 13 please step up to the
17 podium and introduce yourself? Please state your
18 name and any organization you're representing for
19 the record.

20 MR. TYNE: Good afternoon. My name is
21 Brendan Tyne. Thank you for the opportunity to
22 speak before you today. My travel and lodging have

1 been provided by Acadia. However, I have no
2 further financial relationship with the company,
3 nor do I stand to profit from the approval of
4 pimavanserin.

5 It is with great sadness that I stand before
6 you today. I am not an emotional person, but I cry
7 at least once a day over what this disease has done
8 to my mom and to our family. My mom was diagnosed
9 with Parkinson's in 2014. When my father called
10 and told me, I was unable to breathe or speak.

11 This is impossible, I thought to myself. My
12 mom was a rock, always in great health, looked 10
13 years younger than her actual age would suggest;
14 the kindest, more caring mother a child could ever
15 ask for. This can't happen to her.

16 I finally choked out the words "I will call
17 you back," and then I hung up. After I collected
18 myself, I called him back, and we began the
19 discussion around what this meant for my mom and
20 how long before she starts showing real signs of
21 this horrific disease. My father was having health
22 issues of his own at the time, and still is, so the

1 thought of him serving as the primary caretaker for
2 his wife of 50 years was a daunting task, to say
3 the very least.

4 Early on, the focus was on the physical
5 aspect, although my mom had already shown signs of
6 the mental effects. Over the next year, she
7 declined slightly, but not rapidly. It wasn't
8 until the past few months that things have gone
9 downhill dramatically. My mom cannot move without
10 assistance and has hallucinations almost constantly
11 throughout the day.

12 She thinks there are people in the house and
13 animals are coming to get here. One night while I
14 was there to help out, my dad woke me up in the
15 middle of the night because my mom had fallen out
16 of bed and could not get up without our help. My
17 dad has to take care of her every minute of every
18 day. She yells at him when he tries to help and
19 cries herself to sleep every night because she
20 thinks he's trying to harm her.

21 My parents have been happily married for
22 50 years. They are the epitome of a loving couple

1 and a true example of what it means to be married.
2 Their 51st anniversary is next month, and I can
3 only assume my mom won't even know what it means.

4 My dad is so distraught that on Christmas,
5 he broke down in my arms, sobbing about how much he
6 loves her and can't stand to see her go through
7 this. He is also not an emotional person, so to
8 see him like this shows just how much it is tearing
9 him apart.

10 On top of taking care of my mom, my dad now
11 has to sell the house that they have lived in for
12 43 years, raised our family in -- and it's the only
13 place my mom has ever considered home -- because it
14 is now unlivable for her. He then has to find a
15 new place to live, all this while he considers the
16 financial implications, healthcare options, deals
17 with insurance, takes her to the doctor, and gets
18 the appropriate people in to help her.

19 Given that these are all things my mom has
20 taken care of throughout their marriage, it is
21 impossible to overstate how much stress this is
22 adding to my dad's already unconscionable

1 circumstances.

2 I have two young children that love their
3 grandmother. If nothing is done to bring her back
4 to some semblance of normalcy, my children will
5 never remember their grandmother for who she really
6 is, a loving, funny, caring woman who has improved
7 the lives of all of the loved ones who surround
8 her.

9 Please, I beg you, do not deprive my
10 children and their grandmother of experiencing that
11 love. Please recommend approval of pimavanserin
12 for my mom and so many others who suffer with
13 Parkinson's disease hallucinations. Thank you.

14 DR. BRENT: Thank you.

15 Will speaker number 14 please step up to the
16 podium and introduce yourself? Please state your
17 name and any organization you're representing for
18 the record.

19 DR. KREMENS: May it please the committee,
20 my name is Daniel Kremens, and I'm an associate
21 professor of neurology and the co-director of the
22 Parkinson's disease and movement disorder center

1 and Sidney Kimmel Medical College at Thomas
2 Jefferson University. I currently personally care
3 for hundreds of patients with Parkinson's disease.

4 Although I have been a paid consultant to
5 Acadia in the past, I have no equity interest in
6 the company, and I am appearing today before this
7 committee on my own time to express my deeply felt
8 concerns regarding Parkinson's disease psychosis,
9 one of the greatest unmet needs for Parkinson's
10 patients.

11 Parkinson's disease psychosis is one of the
12 dirty secrets of Parkinson's disease. It is not
13 discussed by patients who are concerned that their
14 spouse, children, or doctor will think that they
15 are crazy if they say they are seeing or hearing
16 things. And as insight is lost to the
17 hallucinations or delusions, as happens most of the
18 time in this condition, it becomes devastating to
19 the patients and their families, often leading to
20 nursing home placement and increased mortality.

21 Mr. Smith is a typical patient, and his
22 story highlights the impact that Parkinson's

1 disease psychosis can have on patients and their
2 families. He was an otherwise healthy 80-year-old
3 gentleman when I initially diagnosed him with
4 Parkinson's disease and started him on
5 carbidopa/levodopa.

6 After a year or so, he complained of
7 worsening motoric issues, so his medication was
8 increased. At his next visit, his 83-year-old wife
9 raised the issue that Mr. Smith was accusing her of
10 having intercourse with an 85-year-old neighbor
11 multiple times during the day while Mr. Smith was
12 at work. Mr. Smith admitted that he was angry with
13 his wife and could not believe that she would do
14 this to him after 50 years of marriage.

15 No amount of counseling could shake
16 Mr. Smith's delusions, and Mr. Smith was not
17 demented. He was still a very successful
18 businessman. Over the next year, I tried every
19 intervention, including ruling out infections,
20 reviewing his non-Parkinson's disease medications,
21 reducing his dopaminergic medicines, which he
22 didn't tolerate; adding quetiapine, which made him

1 too tired and confused; suggested clozapine, which
2 he refused due to the necessary blood work.
3 Indeed, the suggestion of blood work only increased
4 his paranoia regarding his wife. I tried
5 risperidone, which caused marked motoric worsening
6 and sedation. Nothing helped, and to make matters
7 worse, Mrs. Smith was diagnosed with an aggressive
8 form of cancer.

9 She was shortly on home hospice, and while
10 she was dying, Mr. Smith routinely accused her of
11 continuing to engage in sexual relations with a
12 neighbor. This caused tremendous pain to Mr. and
13 Mrs. Smith, as well as their daughter who is now
14 bringing Mr. Smith to his visits.

15 Soon thereafter, Mrs. Smith died, and no one
16 was at peace; not Mrs. Smith, who while dying was
17 berated by the accusations of her husband; nor
18 Mr. Smith, who to this day does not understand the
19 betrayal he believes he suffered by his spouse's
20 alleged infidelity; nor his daughter, who often
21 weeps at her father's appointments while he rages
22 against his dead wife.

1 Before becoming a physician, I practiced law
2 at a large New York law firm for nearly seven
3 years. I changed my career because I wanted to
4 help people and have a direct, meaningful impact on
5 their lives. Taking care of Parkinson's patients
6 has been remarkably satisfying, and we have made
7 tremendous strides in the motor symptoms of
8 Parkinson's disease.

9 But despite these wonderful advancements, I
10 still have no safe and effective medication
11 approved for Parkinson's disease psychosis.
12 Current off-label options are either poorly
13 tolerated, lack efficacy, or have serious safety
14 concerns.

15 Pimavanserin has demonstrated to be
16 generally safe, tolerable, with clinical meaningful
17 efficacy. We must recognize the desperately unmet
18 needs and offer hope to our patients and caregivers
19 who are suffering now. I urge this committee to
20 approve pimavanserin for Parkinson's disease
21 psychosis. Thank you.

22 DR. BRENT: Thank you.

1 Will speaker number 15 step up to the podium
2 and introduce yourself? Please state your name and
3 any organization you're representing for the
4 record.

5 MR. THOMPSON: Hi. Ted Thompson, president
6 and CEO of the Parkinson's Action Network. Because
7 Drew Bourrut was unable to be here, I am standing
8 in for him while you view the video that he
9 submitted.

10 (Video played and transcribed.)

11 MR. BOURRUT: I'm Drew Bourrut and live in
12 Smithtown, Long Island, New York. I have no
13 financial relationship with Acadia and will not
14 gain financially should pimavanserin be approved by
15 the FDA.

16 My wife several years ago had many episodes
17 of hallucinations, hallucinations, delirium,
18 illusions. It was dangerous. She woke up one
19 night, middle of the night. She was in a dream but
20 couldn't tell that she now had woken up; thought
21 she was going to be killed; raced down our hall.
22 And people with Parkinson's can't race, but she

1 did.

2 I caught her at the front door. She said,
3 "Am I dead yet?" Collapsed on the floor. It took
4 a couple of hours of talking her down before we
5 could go back to bed. And after that, for months I
6 didn't sleep right because I never knew whether
7 tonight would be a night when she would have one of
8 these episodes.

9 She also became afraid of her house. When
10 we would go out, when we came home, she would look
11 in our front windows and see it filled with people.
12 Of course, they weren't there, but she became more
13 and more uncomfortable.

14 So when Dr. Kreitzman told us about the
15 possibility of this experimental drug, we went into
16 the double-blind study. And it became very clear
17 very quickly that Laura was on the actual drug
18 because within a month, the hallucinations, the
19 delirium, the illusions were gone.

20 She still gets them occasionally. But now
21 she knows that they're hallucinations or illusions,
22 primarily illusions, and she's no longer afraid of

1 them because she was just terrified of them.

2 So I really hope that the FDA approves this
3 drug because there are a lot of people out there
4 that have to be on -- who can use this. And it has
5 been just wonderful for my wife.

6 DR. BRENT: Thank you. I'd like to thank
7 all the speakers for their remarks.

8 The open public hearing portion of this
9 meeting is now concluded, and we will no longer
10 take comments from the audience. The committee
11 will now turn its attention to address the task at
12 hand, the careful consideration of the data before
13 the committee as well as the public comments.

14 Dr. Stankovic wanted to address some
15 questions that had been raised that he can now
16 respond to.

17 DR. STANKOVIC: There were a few questions
18 that stayed open, and we have a few answers to
19 that. There was a question about sponsor's
20 calculation on the NNT and NNH, and there were some
21 different interpretation of those numbers and
22 questions about meaning and how to interpret that.

1 We have with us Dr. Les Citrome, who is a
2 recognized expert in the NNT and NNH calculations,
3 and I wanted to ask him to provide a few
4 clarifications on the ways how we calculated and
5 how we think about that.

6 DR. CITROME: Thanks very much. Good
7 afternoon. My name is Les Citrome. I'm a clinical
8 professor of psychiatry and behavioral sciences at
9 New York Medical College in Valhalla, New York.
10 I'm being compensated by Acadia as a consultant.

11 I'm a big fan of number needed to treat,
12 number needed to harm, and made it a focus of my
13 career for the past 10 years, and I've written
14 extensively on this topic.

15 NNT and NNH are tools that clinicians use to
16 try and appraise clinical trial results and are
17 used to assist in explaining these to patients.
18 And I just wanted to clarify some of the points
19 being made earlier today about the calculation of
20 number needed to harm in particular.

21 It's something that I ordinarily calculate
22 for commonly encountered harms when used to assess

1 the day-to-day decisions that we have when using
2 one drug or another. For example, for
3 antipsychotics, thinking about the rate of
4 sedation, akathisia, weight gain of at least
5 7 percent from baseline, et cetera. And then to
6 sort of look at these because they are precise.
7 They are commonly encountered enough so that the
8 95 percent confidence interval is relatively
9 realistic and interpretable.

10 So for example, recently approved drug for
11 the adjunctive use for major depressive disorder
12 has a number needed to treat for response of
13 12 -- not all that great, but with a difficult
14 disease like major depressive disorder that has not
15 responded to SSRIs or SSNIs, we'll go for
16 that -- and the number needed to harm for akathisia
17 of 16.

18 If we take that ratio, we call that the
19 likelihood to help or harm, 16 divided by 12, close
20 to 1. So I do warn my patients about expecting
21 possibly to encounter akathisia, but chances are
22 they'll achieve a response more commonly.

1 So there's a relatively high degree of
2 certainty with those estimates. Unusual, uncommon
3 harm such as death are difficult to quantify from
4 randomized clinical trials because the numbers are
5 very small. Thus, the 95 confidence interval is
6 usually very, very imprecise. It contains
7 infinity, which means it's not statistically
8 significant, and we can say that it would take an
9 infinite number of patients to be randomized to the
10 test drug versus placebo before expecting to
11 encounter one additional outcome of death. Of
12 course, that's an extreme example, but that's what
13 the data can tell us.

14 When we try to take the ratio of number
15 needed to harm to number needed to treat, the
16 likelihood to help or harm, with such an imprecise
17 estimate of number needed to harm, it is possible
18 that you are infinitely times more likely to
19 encounter the benefit rather than the harm, which
20 of course, is nonsense.

21 So what we need to do is exercise extreme
22 caution when calculating ratios of likelihood to

1 help or harm, NNH over NNT, be extremely careful
2 when using any data that is so imprecise that it's
3 not statistically significant.

4 So I wanted to make that point, and to
5 address the clinical issues, I want to ask
6 Drs. Isaacson and Ballard to come up.

7 DR. BALLARD: Thank you. I just wanted to
8 apologize that we didn't fully address the question
9 about what the severity scores meant on the scale.
10 As was highlighted earlier, there were nine items
11 on the SAPS-PD with a total possible score of 45.
12 In my experience, I've never seen a person with
13 nine different psychotic symptoms. Those are a
14 range of potential hallucinations and delusions
15 that a person might experience.

16 Usually if a somebody has severe psychotic
17 symptoms, they might have one or two hallucinations
18 and perhaps an accompanying delusion. The normal
19 way that we would perceive that to be severe is on
20 the basis of the severity of the individual
21 symptoms, which is quantified on the naught to 5
22 scale. So with that particular scale, if a score

1 of 5, an individual symptom means that that symptom
2 is present daily and very impactful. So one or two
3 symptoms at that level of severity would be severe
4 psychotic symptoms in clinical practice.

5 Just two very brief other things. We heard
6 mention of the clozapine studies for Parkinson's
7 psychosis, and Dr. Andreason mentioned the
8 open-label extension of that study. I'd just like
9 to clarify that in 60 patients over 12 weeks, there
10 were actually 6 deaths in that open-label
11 extension. I think that's important to
12 acknowledge.

13 Finally, Dr. Stone mentioned the ratio of
14 harm for mortality with atypical antipsychotics in
15 Alzheimer's disease from the meta-analysis. I'd
16 just like to clarify that that wasn't the only
17 consideration in terms of the benefit-harm ratio
18 because the meta-analysis of the same studies for
19 psychosis suggests that the effects size measured
20 by Cohen's d is actually less than naught, .2. So
21 actually the drugs aren't effective as well as
22 being harmful.

1 DR. ISAACSON: I think that the question
2 about whether these patients truly are moderate or
3 severe, I think as we see in the videos and the
4 patients and the stories that we've heard so
5 eloquently, we can see that even these scores on
6 scales are just a surrogate measure really. The
7 impact on patients, their caregivers, their daily
8 lives, their family, is so immense that these
9 patients who testified by video and such and met
10 entry criteria had a mean of 15, but their symptoms
11 were moderate to severe in how they affected them
12 and their caregivers and their lives.

13 I think the other point to be made simply is
14 that this psychosis is not happening in a vacuum.
15 It's happening in people with Parkinson's and
16 impaired mobility. And every two, three, or four
17 hours, their mobility gets better, then it gets
18 worse, and they can't move. And then they take
19 their medicine, it may work, and they get better,
20 or it may not work so well and they stay immobile.

21 This happens four or five, six
22 times a day. And it's on these patients where they

1 have these terrible psychosis symptoms that you
2 just heard so much about.

3 DR. STANKOVIC: A couple of other questions,
4 a question on the videotapes or the live interviews
5 done by Medavante, our contractor, there were a
6 sample of interviews taped, primarily for the
7 quality inter-rater reliability purposes, and that
8 is how the high inter-rater reliability of .93 was
9 established. As a routine procedure and for
10 privacy reasons, these sample tapes are later on
11 destroyed after the project is completed.

12 The question on the PD medications and
13 protocol violation, we had 4 patients that modified
14 their PD medication during the trial. Analysis,
15 when these 4 patients are excluded from the trial,
16 there was no effect on the primary outcome or the
17 outcome of the trial.

18 **Questions to the Committee and Discussion**

19 DR. BRENT: Thank you. We'll now proceed
20 with the questions to the committee and panel
21 discussions. I would like to remind public
22 observers that while this meeting is open for

1 public observation, public attendees may not
2 participate except at the specific request of the
3 panel.

4 We will be using an electronic voting system
5 for this meeting. Once we begin the vote, the
6 buttons will start flashing and will continue to
7 flash even after you've entered your vote. Please
8 press the button firmly that corresponds to your
9 vote. If you are unsure of your vote or you wish
10 to change your vote, you may press the
11 corresponding button until the vote is closed.

12 After everyone has completed their vote, the
13 vote will be locked in. The vote will then be
14 displayed on the screen. The DFO will read the
15 vote from the screen into the record. Next, we'll
16 go around the room, and each individual who voted
17 will state their name and vote into the record.
18 You can also state the reason why you voted as you
19 did if you want to.

20 We will continue in the same manner until
21 all questions have been answered or discussed.

22 I just wanted to clarify one thing for us to

1 consider, which is that it appears that for the
2 subgroup with dementia, that the risk/benefit ratio
3 was more favorable. And I don't know if we need to
4 discuss that further, but that was just an
5 observation that I think we should keep in mind.

6 (No response.)

7 DR. BRENT: You can see that I'm following
8 directions well here.

9 Has the applicant provided substantial
10 evidence of the effectiveness for pimavanserin for
11 the treatment of psychosis associated with
12 Parkinson's disease? So we're discussing now.

13 Dr. Gerhard?

14 DR. GERHARD: It's again a question for the
15 sponsor. We had some discussion about the problem
16 in looking at an average score of a -- and how to
17 interpret the reduction when the severity in a
18 sense can -- as Dr. Ballard just pointed out -- may
19 lie in a single symptom or in one or two symptoms.

20 So a patient might be very severely impaired
21 with a score of 10 if he has two subscales that are
22 at 5, and that person might be significantly helped

1 if he has a 5 in a symptom category and that goes
2 down to 3. The same would happen to another
3 category.

4 That would be very different, I think, than
5 a patient that has five subscales at 3, and he goes
6 down to 1 in four of them.

7 So is there any way that you have looked at
8 this in the sense of improvement, how much of that
9 average affects specific symptom categories or
10 would lower the kind of maximum points in those
11 5-point subscales?

12 If I understand correctly what Dr. Ballard
13 was saying, that's really where the severity lies.
14 Rather than the sort of 5 driven by a 1 on five
15 subscales would be very different than a 5 on one
16 specific subscale. I'm not quite sure whether
17 there's a better way to look at that.

18 DR. OWEN: So the question that I'm
19 understanding is have we looked at it by how many
20 people got better on a one subscale versus those
21 who got better on multiple subscales.

22 DR. GERHARD: Whether the average

1 improvement was kind of focused on specific
2 subscales where there was a meaningful improvement,
3 or whether it was kind of more commonly distributed
4 over five, six, seven subscales, where I think the
5 interpretation of the two different scenarios would
6 be very different.

7 DR. STANKOVIC: The items on the 9-item
8 scale that changed most was the hallucination
9 global item, visual hallucinations and the global
10 item on delusions. Slide up, please.

11 So as you can see, these are first, second,
12 and then third from the bottom are changes on those
13 items. I will remind you that in the entry
14 criteria for the trial, the requirements on the
15 SAPD-PD was that minimum one item has a score of 3
16 and one global item has a score of 3 or more.

17 DR. GERHARD: Just for clarification, this
18 is not -- this is just the raw treated group
19 baseline and post-treatment without placebo --

20 DR. STANKOVIC: Yes. This is without
21 placebo.

22 DR. TEMPLE: Do you have a similar slide

1 that shows effect size for each of those? That is,
2 difference between drug and placebo. That's what
3 you're really asking.

4 DR. STANKOVIC: We do not.

5 DR. BRENT: Dr. Duda?

6 DR. DUDA: John Duda. Actually, I think
7 what he's really trying to get at is do you have a
8 similar slide looking at, for example, how many of
9 the people responded had a greater than 2, say,
10 improvement on a given item, so greater than two
11 steps on visual hallucinations or anything like
12 that?

13 The one clinical example you gave did have a
14 2-point -- and I think going from once a day to
15 once a week is a clinically meaningful response,
16 and that would be an indicator of that.

17 DR. STANKOVIC: We do have cutoffs from 1 to
18 10 change on the SAPS-PD scale in the score in the
19 pimavanserin arm and placebo arm. We do not have
20 for the individual items, but we do have for the
21 total score from distribution of patients that had
22 one or two or three or so on reduction.

1 DR. BRENT: Dr. Sarkar?

2 DR. SARKAR: This is just a comment to the
3 sponsor. In my reading of the participants in the
4 trial, there were two who were not white, and I
5 feel that that makes the generalizability very
6 limited for those of us who are practicing here.

7 DR. OWEN: I'm sorry. Can you repeat, there
8 were two who were?

9 DR. SARKAR: Who were not white by race or
10 ethnicity. Not white.

11 DR. OWEN: In terms of the generalizability
12 of the general population. So we've looked at this
13 from a different perspective. There is a Kaiser
14 database analysis in 1990s of 588 patients, new
15 incidence patients, to get at this idea of
16 demographics in the PD patients.

17 What we're seeing, or at least what was
18 demonstrated in that study, was that the
19 demographics of the patients who are treated or
20 diagnosed and treated for Parkinson's may not be
21 exactly the same as the demographics of the overall
22 population.

1 Slide up, please. So this is from that
2 Kaiser database. Eighty percent in that population
3 are white; 5 percent black.

4 I'd like to invite Dr. Stankovic to talk
5 about subgroup analyses by demographics.

6 DR. STANKOVIC: I would just want to say
7 that in the clinical trials, the demographic
8 proportion of patients in regard to different
9 demographic characteristics obviously depends on
10 the geographic area where we do. In our overall
11 program, we had about 10 percent of patients that
12 are non-white. Part of that is because also one of
13 the trials was done in India, so we had patients
14 there.

15 The overall demographic proportion, we would
16 think that the representativeness of the sample
17 that we have comes close, but it's not really where
18 it should be.

19 DR. SARKAR: I think it's a little bit
20 disingenuous to show a slide from 1994 and '95 in
21 one healthcare system and say that that's what
22 we're doing with Parkinson's. I understand that

1 recruiting diverse participants for trials is not
2 easy, but I'm disappointed by that response.

3 DR. BRENT: Dr. Winterstein?

4 DR. WINTERSTEIN: I have a question for the
5 FDA, I guess, in thinking through what efficacy and
6 what safety data we have. We're looking at one
7 phase 3 study now, which I understand could be
8 considered under the Breakthrough Therapy
9 Designation Act, but I see concerns on both sides.

10 With the efficacy portion, we have
11 essentially an untested scale in which we learn now
12 has a massive floor effect because it appears that
13 there would be really no patients who would have a
14 45 score. So that still to me seems to be some
15 hand-selected scale that we don't know really what
16 it means in the context to other drugs that have
17 been tested in this context. And just comparing
18 effect sizes doesn't really seem to address that.

19 So we have a scale that there's no
20 test/retest reliability that has been done to
21 summarize what Dr. Schmid had asked about. We
22 don't really know the psychometric properties of

1 this scale. So that's the efficacy portion.

2 Then obviously, from the safety portion, we
3 really don't have enough data. Of course, we never
4 have when we're looking at phase 3 studies. But
5 I'm wondering what the thoughts are on requiring a
6 second trial, considering I have never dealt with
7 the breakthrough designation before. So I'm
8 curious whether that would be an option.

9 DR. TEMPLE: Let me start. The concern
10 about the measurement would still be there even if
11 you had two studies, and that's one of the reasons
12 we're coming to --

13 DR. WINTERSTEIN: The scale could be
14 changed.

15 DR. TEMPLE: Well, that's a different
16 question. I mean, this study used a number of
17 scales in addition to the primary endpoint, and one
18 of the things that we're coming to the committee
19 for is advice on whether you think that's a
20 credible measurement.

21 All I'm saying is that the two-study/one-
22 study question turns mostly on whether one study

1 can be persuasive. And we've written about this,
2 and we've said, ordinarily, we expect more than one
3 adequate and well-controlled study to support a new
4 claim using appropriate endpoints and all that, but
5 that if the effect size is -- if the effect is
6 statistically very significant, and we give an
7 example of like .001, we can choose to rely on a
8 single study. So we can.

9 But you're raising questions about what the
10 scale means, and I'm not the person to answer that.
11 I think Mitch or others need to address that, but
12 replicating it won't make the scale better.

13 Now, there might be another scale someone
14 could use, but I think you need to talk about that.
15 I mean, they do use a global also. They had
16 several scales, and they show similar results. But
17 whether we rely on one study is usually a matter of
18 how persuasive the statistics of the finding is.
19 And when we talked to the company, we told them
20 that a very persuasive single trial could be
21 considered to support effectiveness.

22 But the question of whether you like the

1 scale, whether you think it's valid, whether you
2 think it's credible, that's not for me to say.
3 That's why we're here.

4 DR. WINTERSTEIN: The reason I bring this up
5 is a second trial would provide the opportunity of
6 changing that. I mean, we have a scale that
7 doesn't have any formal psychometric testing. I'm
8 a little bit surprised about relying on a scale
9 like that as the primary efficacy tool.

10 DR. TEMPLE: Well, it was measuring two
11 aspects of the psychiatric problem, and I think one
12 has to decide whether you think it's a good
13 measurement of that, because measuring
14 hallucinations, that's one of the major problems.
15 If you don't think that's a good scale, it's
16 important to think of what would be a better scale.

17 DR. CHEN: Yes. This is Wen-Hung Chen. I'm
18 from the clinical outcomes assessment staff.

19 SAPS H plus D, the whole 20 items instrument
20 has been used in schizophrenia. It was developed
21 for schizophrenia and has been used primarily in
22 the schizophrenia patient population. There are

1 some little research that supports its psychometric
2 properties.

3 To support for the psychosis in the
4 Parkinson's disease, we have that one study, one
5 paper that was done in showing that reducing from
6 the 20 items to the 9 items. And that one shows
7 some psychometric properties in terms of some of
8 the reliability, correlation with other
9 instruments.

10 However, like you said, we don't feel it is
11 ideal, but it is acceptable for this indication
12 because of the breakthrough therapy designation and
13 because of some of -- the 9 items cover some of the
14 important relevance in terms of psychosis for
15 Parkinson's disease. So that's why we feel that it
16 is adequate, not ideal, but it is adequate.

17 We do feel that further improvement in that
18 instrument would be actually even better for the
19 future. But again, for this submission, we feel
20 that it is sufficient to demonstrate that it does
21 cover some of the important symptoms that we are
22 concerned about.

1 DR. MATHIS: We should point out, too, that
2 the 20-item scale was also significantly different
3 drug versus placebo in this trial. So while we'll
4 never be sure if the 9-item -- well, someday in the
5 future, we hope to be more sure that the 9 items
6 capture what we're interested in. The fact that
7 the 20-item scale may be one that's been around
8 longer and has had its psychometric properties
9 evaluated made me feel better about that.

10 DR. BRENT: Thank you. Dr. Narendran?

11 DR. NARENDRAN: My question is somewhat
12 related, but not exactly perhaps. But one of the
13 things is, I mean, this drug seems to be no worse
14 or no risky than antipsychotics for dementia based
15 on the presentation.

16 So then the question really is, I mean, is
17 it as effective? I mean, what's clinically
18 meaningful? It's statistically significant, but is
19 the 3 point clinically meaningful? I guess that's
20 where the struggle I've been having is.

21 So it's hard because there are no literature
22 to compare, and the scales used in schizophrenia

1 trials, BPRS or PANSS, you can't really normalize
2 and say this is where this stands.

3 The CGI seems to be a secondary measure.
4 The delta compared to the drug to the placebo is
5 only .6 or .5. Is that norm in schizophrenia
6 trials to see that small of a difference? Because
7 it seems like that could be something that could be
8 used to see how effective this drug could be or how
9 clinically meaningful it could be.

10 I'd also like to hear from the neurologists
11 on this panel to maybe clarify for the
12 psychiatrists like us what is clinically
13 meaningful, if this small number, 3 points or what.

14 DR. DUDA: John Duda. As one of the
15 movement disorder neurologists here, I want to
16 start out by saying I think from my perspective,
17 and maybe Stan would agree, that the subdivision of
18 the full SAPS-HD into the SAPS-PD has face
19 validity. I mean, the symptoms that they pulled
20 out don't seem to be just cherry-picked because
21 they had the most likelihood of showing an effect.

22 Those are the ones that are most commonly

1 seen in PD. Like I think they pointed out, if we
2 had everything we wanted, we'd have a totally
3 different scale that included some of the symptoms
4 that aren't captured at all in there like illusions
5 and presence hallucinations.

6 But I don't know, from my perspective, we
7 keep talking about whether or not the clinically
8 meaningful difference of 3 points is valid, but
9 it's 3 points over placebo. I mean, to me as a
10 clinician, it's a 6-point difference, right? It's
11 6 points from baseline to treatment effect.

12 Yes, to prove that it's better than placebo,
13 we have to look at the 3-point difference, but to
14 determine whether or not it's clinically
15 meaningful, I think we should focus more on the
16 6-point difference between baseline and the benefit
17 of the treatment.

18 In that case, like I said, it would have
19 been really nice to see how many patients had a
20 significant improvement on one of those 9 different
21 items. But presumably with an average of a 6-point
22 benefit, I think probably a fair number of them

1 probably wouldn't have at least a 2-point
2 difference on one of those items. I could be
3 wrong, but that's my perspective.

4 DR. BRENT: Dr. Grieger?

5 DR. GRIEGER: I'm going to speak directly to
6 the question. I mean, I think they've demonstrated
7 efficacy, and I think the big differential with
8 this, compared to what we've got now, is the
9 absence of any evidence of a motoric impairment as
10 a result of adding this medication to patients that
11 were already on Parkinsonian medications.

12 So that's a big plus for this population.
13 It's a difficult to treat population with a lot of
14 primary effects and a lot of side effects in a
15 complex medication regimen. And it showed it
16 didn't cause any harm. And for a number of
17 patients, it showed marked improvement in some
18 symptoms.

19 To the extent that this is a very pervasive
20 problem in Parkinsonian patients, any
21 improvement -- I mean, a 3-point improvement to me
22 is big deal. If you go from having a symptom every

1 day to having a symptom twice a week, that's a huge
2 improvement.

3 I didn't have a problem with the scale for
4 the same reason that you mentioned, that it was
5 derived from their prior studies of what actually
6 shows up.

7 It's a lot easier -- I use a lot of
8 clozapine, but I work in a hospital so it's easy to
9 use clozapine in a hospital. It's really hard with
10 patients that can't get out to be able to do the
11 lab tests.

12 So this really fills a niche that nothing
13 else is approved for that's easy to use. And
14 whether it's caused by the addition of the drug or
15 whether it's just that the patients were getting
16 worse and required the drug, there's a study that
17 just came out this week on hazard ratios of
18 patients that are started -- 7,000 paired groups,
19 7,000 patients paired in each group, who are
20 Parkinsonian patients started on antipsychotics,
21 those not started on antipsychotics.

22 Those started on the antipsychotics,

1 olanzapine, Seroquel, and risperidone had a
2 doubling of their mortality within 180 days of
3 starting on the drug. So that's a problem. It
4 seems that if this drug can do something without
5 doing something bad or not doing it much worse than
6 the placebo, it seems to fill a gap.

7 DR. BRENT: Dr. Duda?

8 DR. DUDA: Can I just respond to that real
9 quick? The study by Weintraub, et al. should be
10 clarified that it's a naturalistic study, so you
11 really can't separate out the effect of the drug
12 versus the effect of having psychosis in
13 Parkinson's disease.

14 DR. GRIEGER: Right, I hope I made that
15 clear, but you're absolutely right. It's a
16 naturalistic study.

17 DR. BRENT: Dr. Ionescu?

18 DR. IONESCU: I just have a brief technical
19 question to ask about number needed to treat. The
20 FDA had a number needed to treat summary slide -- I
21 think it's slide 31 -- compared to slide CE-28 from
22 the company.

1 I was just curious to know, I noticed with
2 the company, there wasn't a greater than or equal
3 to 50 percent reduction in the SAPS-PD analysis.
4 And I just wanted to make sure it would be the same
5 numbers that the FDA presented on their slide. I
6 just wanted to make sure.

7 DR. STANKOVIC: The numbers that we
8 presented are based on the all-20 clinical trial.
9 FDA, Dr. Andreason presented both that and then
10 exploratory analysis that he did while including
11 the other trials that were not either completed or
12 failed.

13 DR. IONESCU: Okay. Thanks.

14 DR. BRENT: If there aren't any further
15 comments -- oh.

16 DR. SCHMID: I was just wondering if there
17 was any data on long-term efficacy beyond 6 weeks.

18 DR. STANKOVIC: Yes. In addition what we
19 presented, we do have data for all of the patients
20 that converted from the double-blind trial into
21 open-label trial. We still kept following
22 enrollment in the open-label trial. We still kept

1 separation of their prior randomization in the
2 trial, and here is the data. I would like to point
3 out that, obviously, we are looking at long-term
4 uncontrolled data.

5 Slide up. As you can see, similarly what we
6 present up to 10 weeks, the people in gray that
7 were on placebo, within the first 4 weeks of the
8 open-label trial, came to similar efficacy as the
9 patients that were in the pimavanserin arm in the
10 double-blind trial. And then pretty much up to
11 30 weeks, they maintained that.

12 These are the patients in study 020 that
13 converted into the trial. We have another
14 graphic -- slide up, please -- presenting all
15 patients from all trials that are in the open-label
16 trial, and this is their efficacy data.

17 Once again, as we go further into here, we
18 have a pretty good retention because up to week 30,
19 we lost about -- we have retained 75 percent of the
20 patients up to week 30. But as we go further, we
21 have data obviously for longer, but the dropout
22 rates continued to creep up. Although, like I

1 said, for this type of trial in psychosis, up to
2 30 weeks, retention of 75 percent is quite
3 impressive, actually.

4 DR. SCHMID: So let me just summarize that.
5 So it looks like for the CGI outcome at 30 weeks,
6 there was no difference between the two groups.
7 And do you have the primary outcome? Do you have
8 any information on primary outcome?

9 DR. STANKOVIC: Primary outcome was only
10 measured after first 4 weeks. Later on, it was
11 only a CGI, the Clinician Global Impression.

12 DR. PICKAR: Question to the agency, to you
13 folks, the way it's phrased, is effectiveness for
14 the treatment of psychosis associated with
15 Parkinson's disease. And not to beat the old
16 horse, but really what you're treating is psychosis
17 associated with treatment of Parkinson's disease.
18 There's no untreated person in this study.

19 As I know broadly, but not being a
20 neurologist, that it's not common to see a
21 psychosis associated without some treatment. And
22 what you're doing is you're giving dopaminergic

1 agents, which are known at every level, according
2 to the FDA, that one of their side effects is
3 hallucinations and delusions. It's in the package
4 insert for levodopa and probably is for the
5 dopamine agonist.

6 So my question, is this phrased correctly
7 because that doesn't sound -- it seems to me that
8 you're treating a drug side effect, and I don't
9 know if that's overly picky. I'm willing to hear
10 other people's opinions. But it just is a little
11 bit funny the way it's stated here. And I don't
12 think the data demonstrate that, but they do
13 demonstrate improvement when you get these kind
14 of -- I'm calling them side effects unless
15 neurologists would tell me otherwise.

16 I don't know how else to interpret these
17 psychotic symptoms treated with -- I don't even
18 know dosages, but presumably pretty aggressive
19 dosages of Sinemet over many, many years.

20 So I just want to know, is this statement
21 actually correct, assuming that the data says,
22 gosh, it's really doing the deed? Is this

1 statement even correct?

2 I'm looking at the neurologists. I always
3 like putting them on the spot. But seriously, what
4 we're treating, is this Parkinson's disease or is
5 this drug-induced adverse events or symptoms? And
6 the drugs involved are known, certified by the FDA,
7 to produce hallucinations and delusions. And it
8 has broad implications to how this drug is going to
9 be used by clinicians. That's why I'm saying it.

10 People will use it off label in a much more
11 broad way if you leave it in this, affecting the
12 psychosis of an illness versus a drug-induced
13 psychosis. It will be very different use of this
14 compound. And we heard the sponsor speak a great
15 deal about calling it an antipsychotic. Each time
16 I got a little twitch. Never found out the data in
17 real psychotic patients. But you're looking at
18 psychotic symptoms in drug-treated patients by
19 drugs that cause psychosis.

20 DR. FAHN: So may I address his question?

21 DR. PICKAR: Yes, I'm asking advice.

22 DR. FAHN: So you're absolutely right. I

1 mean, all these people are treated. The drugs
2 themselves are probably contributing, if not the
3 sole cause of the psychosis. Certainly, people
4 with Parkinson's disease, even before they get on
5 medicine, maybe could have some symptoms like with
6 dementia with Lewy body symptoms. They could have
7 hallucinations.

8 But generally, what we see are people who
9 are treated with Parkinson's disease, who then
10 develop their psychosis on the drugs. So is the
11 disease itself causing the psychosis, if that's
12 what you're asking, or is it the drugs that they're
13 treated with causing the psychosis?

14 DR. PICKAR: I'm looking at the -- I'm
15 getting very concrete in my -- I'm looking at the
16 label and what this has proven.

17 DR. FAHN: My interpretation when I read
18 this is that it says, "associated with Parkinson's
19 disease." It didn't say that it's caused by
20 Parkinson's disease.

21 DR. PICKAR: They do not have one patient
22 there without treatment, not one patient.

1 DR. FAHN: But even so, it doesn't -- let's
2 say you had a patient who has psychosis with
3 Parkinson's, and there will be some patients -- if
4 this drug does not worsen Parkinson's disease, it
5 might be a very good treatment for it. Did they
6 have any patients like that? Probably not.

7 DR. PICKAR: The issue is what they've
8 demonstrated. I understand the wish list. I just
9 want to know -- we're asked a very specific
10 question I'm trying to grapple with. Have they
11 substantial evidence for that statement?

12 DR. FARCHIONE: I think that the issue here,
13 the use of the word "associated" is not by
14 accident. We don't know whether it's the disease
15 causing the symptoms or the treatment of the
16 disease that's causing the symptoms, or both. But
17 the fact is that there is psychosis involved, and
18 it is in this population of patients who have
19 Parkinson's disease. So the two, they hang
20 together, and whatever the causation --

21 DR. PICKAR: And they're associated with
22 people who are given drugs that cause psychosis.

1 That's a fact. That's an FDA label. Now, you
2 can't tease it apart. I'm going to be sticky about
3 this. This is going to have huge implications in the
4 real world.

5 DR. FARCHIONE: Right. But I think that the
6 question is not so much what the implications for
7 labeling are going to be because we'll describe the
8 study population and everything like that. The
9 question is just whether or not they have
10 established substantial evidence for the treatment
11 of these psychotic symptoms that happen to be in
12 this population that has Parkinson's disease.

13 DR. TEMPLE: He knows that. He's just
14 worried about how we're going to describe it.

15 DR. FARCHIONE: Yes. But I mean, the
16 labeling is going to be a separate question for
17 later. And like I said, we'll always describe the
18 population that was part of the study.

19 DR. PICKAR: I would have a problem if the
20 label said this, and that's what we're voting on.
21 So I'm very self-centered. How do I vote on this?
22 I would have a problem with this label.

1 DR. TEMPLE: Is that because you're sure
2 it's the drugs that do it?

3 DR. PICKAR: I'm sorry?

4 DR. TEMPLE: Is that because you think it's
5 obvious that it's the drugs that are causing it?

6 DR. PICKAR: No. I just think that's what
7 you're asking, what does the data show.

8 DR. TEMPLE: No, I know but --

9 DR. PICKAR: And that's what it shows.

10 DR. TEMPLE: -- let's say in the end, we
11 don't have enough data on psychosis in people who
12 aren't treated because how do you get untreated
13 people with bad Parkinson's disease?

14 DR. PICKAR: Well, for example, there are
15 200 patients treated with schizophrenia. I didn't
16 hear one piece of data on the same variables that
17 are here. So maybe it's unique to Parkinson's
18 disease. But there's data out there, and that's
19 how it's going to be used, Bob. That's the
20 problem.

21 DR. FARCHIONE: But we also don't know that
22 the psychosis in the same in Parkinson's disease

1 and schizophrenia. Even the way that it manifests
2 is different with more visual hallucinations in the
3 folks with Parkinson's disease, more of these
4 delusions about infidelity. That seems to be a
5 recurrent theme versus the aliens are putting stuff
6 in my brain. It's a different kind of thing. And
7 without knowing the pathophysiology of the
8 individual, it's hard to say.

9 DR. PICKAR: I don't think it's that
10 different.

11 DR. FARCHIONE: I know it's not. I'm
12 just --

13 DR. PICKAR: And too, when L-dopa, when
14 these drugs cause a psychosis, visual
15 hallucinations are common. Those are drug effects,
16 and psychosis is just not that common. When you're
17 starting to do dopaminergic influences, you get
18 organic-like psychosis, which is what this is.

19 DR. TEMPLE: It sounds like you'd like to
20 see it say associated with levodopa-treated
21 Parkinson's disease or something --

22 DR. PICKAR: Yes. I just want it to

1 accurately reflect what the trial is.

2 DR. TEMPLE: Okay. Well, we'll
3 think -- we'll certainly -- we would think about
4 that. That's a good question.

5 DR. PICKAR: Great.

6 DR. MATHIS: Psychosis associated with
7 Parkinson's disease or its treatment; is that what
8 you're thinking?

9 DR. PICKAR: With treated Parkinson's,
10 associated with Parkinson's disease who are treated
11 with dopaminergic agents. Ninety-eight percent
12 were treated with L-dopa.

13 DR. TEMPLE: We'll think about that. It's a
14 good thought.

15 DR. BRENT: Ms. Witczak?

16 MS. WITCZAK: Yes. I was going to reiterate
17 what you said because that's a big concern, because
18 it's one thing if it's -- because that's everything
19 that I've seen and talked with patients, and it is
20 the drug-induced.

21 So if we are going to be giving another drug
22 on top of a drug, I think we need to have that

1 question in here because I think the efficacy on
2 what they showed us is really more about the
3 treatment for Parkinson's disease.

4 Because I can just see the press releases
5 and everything else and the way it will be
6 communicated to the general public if we don't
7 really answer that question upfront and do it the
8 right way.

9 DR. TEMPLE: Can you say more about that?
10 Are you worried that it would be extended to people
11 who don't have Parkinson's disease? I thought that
12 was the worry that was being expressed.

13 MS. WITCZAK: Yes, that's one of my concerns
14 is that it will eventually be used as off label,
15 especially as we know the way things are going in
16 Congress.

17 DR. TEMPLE: Okay. But in that case, it
18 doesn't really matter whether you're treating
19 something that the Parkinson's -- well, maybe you
20 think it does.

21 You're saying if it's only people who are
22 responding to their treatment, then people wouldn't

1 believe that it would work in someone who didn't
2 have Parkinson's disease. But if it was treating
3 the underlying disease, which happens to also be
4 treated, then they might. That's fine.

5 MS. WITCZAK: Yes. I just think we need to
6 be really clear about what we are looking at the
7 evidence for.

8 DR. PICKAR: And when we vote, it has to be
9 exactly as the question you presented us, correct?
10 I'm just asking.

11 DR. TEMPLE: Well, we're listening to what
12 you said about that. We appreciate that.

13 DR. PICKAR: No, I appreciate that. I'm
14 just trying to answer the question to my sense of
15 what the presentation was, what it showed, and what
16 the statement would be. That's all.

17 DR. BRENT: Dr. Duda?

18 DR. TEMPLE: So are you wishing that we put
19 with treated Parkinson's --

20 DR. PICKAR: I can't approve it stated like
21 this. I don't think they've demonstrated that. I
22 think they've demonstrated in what that population

1 is.

2 Bob, this is a breakthrough study. You're
3 doing it one study, not two. You're moving this
4 very fast. I love it. I love it. I'm a doc. I
5 want these things out there, but be careful on the
6 clinical designs and so forth, and be accurate.

7 I was very disappointed I didn't see more
8 data about its treatment in other psychoses. This
9 is a one-shot deal, one study. So if it's a
10 one-shot study, boy, that's got to be good, and
11 there shouldn't be any questions.

12 DR. TEMPLE: Are we allowed to revise the
13 question? Can we?

14 (No response.)

15 DR. TEMPLE: Let's say we're going to
16 interpret that question as meaning "with treated
17 Parkinson's disease." I don't think that's a
18 problem, and we can do that. It refers to "with
19 treated Parkinson's disease."

20 I also want to correct one other impression.
21 Breakthrough doesn't mean you get by with less
22 data. There's been a couple of comments that

1 suggest that's true. The standard for approval,
2 the legal standard doesn't change. We do a whole
3 lot of things to be flexible and encourage good
4 design and all kinds of other stuff, but the legal
5 standard for approval is the same.

6 DR. BRENT: This is David Brent. So my
7 question is, are we rewording the question?

8 DR. TEMPLE: Yes, I would put "treated" in
9 there.

10 DR. BRENT: So I think we should have it in
11 black and white so the people know what they're
12 voting on.

13 MS. BHATT: Right. And if FDA can tell us
14 what you want us to write, we'll make the edits to
15 the question if you want to change the question.

16 DR. TEMPLE: Well, we're doing this on the
17 fly, but how about if we put "treated" in front of
18 Parkinson's disease?

19 DR. PICKAR: How would the neurologists feel
20 about that? Would that be okay with you guys?
21 You're a separate club over there?

22 DR. DUDA: We didn't have a big problem with

1 it before that, frankly.

2 MS. BHATT: Is it possible if we could
3 answer this question and then have a 1A question?

4 DR. DUDA: From a movement disorder
5 neurologist perspective, if you really want to
6 change -- I mean, because I don't know where it
7 ends because you could say Caucasian and you could
8 keep narrowing it down.

9 DR. TEMPLE: We will understand --

10 DR. DUDA: If you really wanted to make it
11 more appropriate --

12 DR. TEMPLE: We will add the word "treated"
13 to it, either in our brains or on there, but that
14 is what you'll be voting on. Okay?

15 DR. DUDA: This is Parkinson's disease,
16 treatment-responsive Parkinson's disease.

17 DR. PICKAR: You've got a drug-induced
18 problem here. That's what I'm saying, and it's not
19 recognized as that.

20 DR. GRIEGER: Are there any? Are there any
21 Parkinson's patients that have hallucinations that
22 aren't under treatment? Does that ever happen

1 where it's proven that it's from Parkinson's?

2 DR. DUDA: You can certainly have patients
3 who have Parkinson's disease develop hallucinations
4 from treatment, and then as part of the management
5 of that psychosis --

6 DR. PICKAR: Not from treatment. How about
7 non-treated?

8 DR. DUDA: You take them off all of their
9 dopaminergics --

10 DR. PICKAR: Yes, yes.

11 DR. DUDA: -- and they can still have
12 hallucinations.

13 DR. PICKAR: How common is that?

14 DR. DUDA: In advanced patients, it's not
15 that rare. It's essentially the same as you see in
16 dementia with Lewy bodies.

17 DR. PICKAR: So associated with dementia of
18 Parkinson's.

19 DR. DUDA: Yes.

20 DR. GRIEGER: So you might want to use this
21 agent.

22 DR. DUDA: You certainly might want to use

1 this agent.

2 DR. FAHN: So what dementia with Lewy bodies
3 is and what Parkinson's disease dementia is, just
4 two ways of looking at it, they're probably the
5 same disease. And people with Parkinson's disease
6 notoriously get dementia usually when they're in
7 their upper 70s or into their 80s. Most people
8 will have dementia, and with their dementia,
9 they'll have hallucinations.

10 If the person wasn't treated, like a person
11 started out with dementia with Lewy bodies, they
12 would have hallucinations. Although this drug
13 wasn't tried on that population, so we can't
14 address it. But this is probably a drug that could
15 be used. It certainly was not going to make their
16 Parkinson's symptoms worse.

17 So that's what's going to happen in the open
18 market, off label. It will be used for that kind
19 of disease.

20 DR. PICKAR: What's going to happen off
21 label is it's going to come to our clinic, and
22 we'll be seeing it psychiatrically; so off-label

1 use in a broad statement, and that's an issue.

2 DR. DUDA: Except for dementia with Lewy
3 bodies, which still comes to us. Dementia with
4 Lewy body patients would still come to movement
5 disorders and dementia specialists, and it's
6 certainly going to be used for that off label, I
7 would expect.

8 DR. BRENT: I think we need to call the
9 question, and my understanding is that we have to
10 call the question as written.

11 MS. BHATT: Yes. If we can answer the
12 question, and then we can just incorporate
13 everybody's comments, and we can put that into the
14 minutes. I think that's going to be a lot easier
15 than reinventing the question.

16 Is that okay? Is that acceptable to the
17 division?

18 DR. TEMPLE: Yes, that's fine.

19 MS. BHATT: Okay. So if the chair could
20 please read the question again.

21 CAPT ANDREASON: I just thought I can pull
22 up a reference to help Dr. Pickar's question.

1 This is from an article by Friedman in 2010
2 on Parkinson's disease psychosis, and the etiology
3 of the hallucinations has been a point of debate
4 for years. Back in 1999, it was thought -- as a
5 matter of fact, when the clozapine article was
6 published, it was published under the heading of
7 Treating Drug-Related Psychosis.

8 In 2010, I quote from Friedman's article,
9 "The most convincing report of hallucinations
10 occurring in untreated Parkinson's disease patients
11 comes from Tanzania where five of 32 patients had
12 hallucinations, primarily of people or faces mostly
13 seen in their homes. Four of these had never been
14 on medications, and the fifth on benzhexol."

15 So nowadays, it's really rare to see
16 somebody who is untreated. And within the first
17 year of treatment, the rate of hallucinations
18 doubles, I think, if I'm getting that number
19 correct. But it goes up significantly within the
20 first year of treatment.

21 DR. BRENT: Dr. Narendran?

22 DR. NARENDRAN: I do want to comment to,

1 Dr. Pickar, your question. Well, I have a comment
2 for your thing.

3 I think etiologically, schizophrenia is
4 definitely a pro-dopaminergic, high dopaminergic
5 disease. But Parkinson's disease hallucinations
6 are also very related to 5-HT2A. There's a couple
7 of PET studies that have shown up regulation of
8 5-HT2A in the brain in PDP. And if you look at the
9 schizophrenia literature, 5-HT2A typically is
10 negative. There is no real finding in PET. And if
11 you think about LSD as a drug, which also has very
12 hallucinogenic effects and more visually linked, it
13 has what you see in PDP and not necessarily linked
14 to psychosis.

15 So I think, mechanistically, they're
16 slightly different. I don't think we should tease
17 apart it. I think that wording as it stands is
18 probably okay.

19 DR. PICKAR: Okay. Thank you.

20 DR. BRENT: Dr. Ionescu?

21 DR. IONESCU: Just one question regarding
22 slide CE-9 from the company. That was the

1 inclusion/exclusion criteria, and this might help
2 with this question, too. I noticed that patients
3 had to have Parkinson's disease for at least a year
4 before coming to the study and then they had to be
5 psychotic for at least a month.

6 Was there anyone enrolled in the study whose
7 psychosis was longer than their Parkinson's
8 disease?

9 DR. STANKOVIC: No, because the criterion
10 was that the first Parkinson's disease occurred
11 prior to the psychotic symptoms, and that is really
12 a diagnostic criteria for Parkinson's disease
13 psychosis.

14 DR. PICKAR: Did you withdraw the people
15 from the antipsychotics before they entered the
16 study, or was that an exclusion criteria? Or did
17 you do that as part of the study? Earlier you said
18 that you stopped their antipsychotic during that
19 period.

20 Were these people who were on the
21 antipsychotics, or whatever, stopped, waited
22 3 weeks, and then added this study? You're making

1 a lot of moving parts in a CNS pharmacology study.

2 DR. STANKOVIC: There was a minority of
3 patients in the trial, about less than 15 percent I
4 believe overall, that were on antipsychotics going
5 into the trial. But they had to stop that
6 antipsychotic at least 5 half-lives prior to
7 randomization.

8 I would like also to point out that that
9 doesn't mean that these patients have never been on
10 antipsychotics. They were just not currently,
11 immediately before the trial, on the antipsychotic
12 treatment.

13 DR. BRENT: Okay. I think we should take a
14 look at the question again. So I'm going to read
15 it again, and I think we should vote.

16 DR. SCHMID: Can I ask a question? Are we
17 discussing before each question? So we're voting
18 on --

19 DR. BRENT: Yes, we're just voting on this.

20 So the question is, has the applicant
21 provided substantial evidence of the effectiveness
22 for pimavanserin for the treatment of psychosis

1 associated with Parkinson's disease?

2 Please press the button on your microphone
3 that corresponds to your vote. You have
4 approximately 20 seconds to vote. My 20 seconds
5 starts after I finish talking, right?

6 Please press the button firmly. After you
7 have made your selection, the light may continue to
8 flash. If you are uncertain of your vote or you
9 wish to change your vote, please press the
10 corresponding button again before the vote is
11 closed.

12 (Vote taken.)

13 MS. BHATT: The voting results, yes, 12; no,
14 2; abstain, zero; no voting, zero.

15 DR. BRENT: We'll go around the room, and
16 each person should say how they voted and why,
17 starting with Dr. Elmore.

18 MS. ELMORE: Susan Elmore. So,
19 obviously -- well, first of all, I voted yes. And
20 there are obviously limitations of this study, a
21 number of variables that we've discussed here
22 today. Some could not be controlled based on the

1 nature of the disease, and these may or may not
2 have had an effect on the outcome and the
3 interpretation of the data, but we really don't
4 know.

5 My vote was based on the totality of the
6 data, but my disclaimer here is that I would have
7 preferred rather than use the word "substantial," I
8 would have used "some" because that's just the way
9 that I look at the data. To me substantial would
10 have been, just as an example, going from a scale
11 of 4 or 5 to a 1 or a zero. So that's my comment.

12 DR. TEMPLE: Can I just comment?

13 DR. BRENT: Yes.

14 DR. TEMPLE: Substantial refers to the
15 evidence, not the effect size, just in legal terms.
16 It means convincing or whatever you want it to
17 be --

18 MS. ELMORE: Okay.

19 DR. TEMPLE: -- not whether the effect is as
20 big as you'd like.

21 DR. SARKAR: I'm Urmimala Sarkar. I voted
22 yes, and I voted yes because I believe that there

1 is a benefit that they've demonstrated with a
2 reasonable degree of certainty. And there is a
3 much larger uncertainty about the potential harms.

4 Therefore, I thought it was more public
5 health forward to approve the drug with the
6 understanding that much more work is needed to
7 ascertain the frequency and severity of the harms
8 that will be associated with it.

9 DR. GERHARD: Tobias Gerhard. I voted yes.
10 I believe the data, despite some concerns about the
11 scale that was used, is pretty consistent with the
12 secondary outcomes and so on. We all would want
13 the effect size to be larger, but it's certainly
14 convincing in the sense that it is there, and it is
15 meaningful.

16 DR. WINTERSTEIN: Almut Winterstein. I
17 voted yes for the same reasons that Dr. Gerhard
18 just mentioned.

19 MS. MORGAN: I'm Linda Morgan, and I voted
20 yes. And the reason is that it seemed effective to
21 me.

22 DR. SCHMID: Chris Schmid. I voted yes.

1 I'm not real convinced with the amount of data.
2 However, given the consistency of the outcomes and
3 also the consistency across the two or three
4 studies they've done, which all seem to at least
5 point in the same direction, I was reasonably
6 convinced.

7 I am still concerned a little bit about the
8 subgroup effects and looking forward to the
9 discussion on that.

10 DR. GRIEGER: Tom Grieger, I voted yes for
11 the reasons I already stated.

12 MS. WITCZAK: Kim Witczak, and I voted no
13 for a couple reasons. First of all, because of the
14 discussion we had earlier with putting treatment
15 associated with Parkinson's disease. Also, with
16 the number of people in this clinical trial, it
17 doesn't seem as it's as robust as it should be.

18 So for those reasons, as well as the type of
19 people that were included, the ethnicity and the
20 background.

21 DR. PICKAR: I voted no for reasons that are
22 obvious. I would have voted yes had you added that

1 word, Bob. So I figured this will at least get
2 your attention to how you spell out the label, and
3 you'll think of me when you do it.

4 (Laughter.)

5 DR. BRENT: I think I can stop laughing now.

6 David Brent. I voted yes. I felt there
7 were multiple conversion scales that all showed the
8 same finding. And of course, we'd like more than
9 one positive trial, but this was the only one that
10 was really designed to take in more severe
11 patients.

12 I was also persuaded by the fact that there
13 really is nothing else, so even if the effects are
14 modest, you have to compare to what is available
15 right now, which, as we've been presented, is
16 nothing.

17 DR. IONESCU: Dawn Ionescu. I voted yes. I
18 thought the medium effect sizes were pretty good.
19 Especially as a depression researcher, I can
20 completely understand how needed new medications
21 are for these difficult to treat conditions.

22 The other thing I want to applaud the drug

1 company for doing is using external raters. I
2 think that's kind of a new thing that's coming
3 online, and I think it's really important. It cuts
4 down on bias. They have nothing to gain from
5 saying that your patients are getting better or
6 worse, and I think that was a really good part of
7 the study design.

8 DR. NARENDRAN: Raj Narendran. I voted yes.
9 I thought the company did a good job and
10 convincingly demonstrated that it was effective.

11 DR. FAHN: Stan Fahn. I voted yes. As was
12 pointed out by others also, there is really nothing
13 out there. This drug does not worsen Parkinson's,
14 which is really key factor.

15 I was disappointed that the efficacy seems
16 less robust than I would have liked. I'm not sure
17 about that. Once we get it in our hands and work
18 with it, we'll see how good it really is. But it's
19 certainly better than nothing. And it does help
20 people, and that's why I voted yes.

21 I was also disappointed with the fact that
22 it was immediate effect. It took about 4 weeks at

1 least to get the improvement to some degree of
2 benefit there. But again, maybe newer
3 classes -- not classes, but newer versions of this
4 drug will come out with more power, and is sooner
5 acting, and so forth.

6 So I think this is a good starting point.
7 I'd like to see it being used for that reason.

8 DR. DUDA: John Duda, and I voted yes. And
9 I think one of the other things that was compelling
10 to me was that these are patients who had an
11 average of three years of psychosis, suggesting
12 that the typical management strategies, including
13 using clozapine and Seroquel, which are effective
14 in many patients, were probably tried and probably
15 failed in a lot of them, so making it an even more
16 convincing argument that this was effective.

17 DR. BRENT: I'd just like to summarize the
18 statements. The majority of us voted for the first
19 question. The general tone was that although we
20 would have liked to have seen a bigger trial and a
21 stronger effect, that in the context of this
22 disease and the lack of other readily available

1 treatments that are easy to use, that this
2 represents a step forward.

3 There was concern raised about whether the
4 question should have been focused on drug-treated
5 Parkinson's rather than Parkinson's per se. And I
6 think that the general tone of the response of
7 people's discussion was that that is how people
8 come to us, at least in the United States. But
9 there was some discussion about how the labeling
10 should be to reflect the fact that in these
11 studies, almost 100 percent of people were treated
12 with some kind of a dopaminergic agent.

13 We're now ready for question 2, and I think
14 we'll follow the same procedure. We'll have
15 discussion first.

16 Has the applicant adequately characterized
17 the safety profile of pimavanserin? So the
18 question isn't whether it's safe or not. The
19 question is whether it's been adequately
20 characterized, right?

21 MS. BHATT: Yes.

22 DR. BRENT: Okay.

1 DR. SCHMID: So here's where I'm going to
2 raise the subgroup question. I think Dr. Brent
3 referred to it earlier. We had the breakdown by
4 the MMSE of 25 greater or less, and I believe the
5 count was 12 to 5 in the higher group, and that
6 would make it 4 to 5, I think, in the lower group.

7 So to me, that's an important distinction,
8 and that would be very important to me in knowing
9 whether this has been adequately characterized or
10 not.

11 DR. DUDA: Maybe I misunderstood, but they
12 did characterize the safety issues in both of those
13 groups. You're just talking about the risk/benefit
14 ratio, which is the next question?

15 DR. SCHMID: Well, I guess what I want to
16 know is whether -- I haven't heard any discussion
17 about the safety being worse in one group than
18 another, and that to me suggests that potentially
19 in the people who are worse off to start with,
20 there's more safety risk than in the other group.
21 So I'd want to know that.

22 DR. BRENT: Dr. Narendran?

1 DR. NARENDRAN: My question to the FDA, in
2 the briefing document, the nonclinical toxicology
3 section said that there's some phospholipidosis in
4 the lung. I mean, presumably the way it was worded
5 there was this would be a short-term treatment.
6 Most of these people, they live for an average of
7 two to three years.

8 But if we're talking about putting younger
9 people, like in their 50s or something, or
10 40s -- early Parkinson's people are put on this
11 drug and they stay on there for years -- that could
12 have an impact. I don't know. How do you tackle
13 that? I don't know if you could -- that wasn't
14 brought up in the morning, so if you could --

15 DR. ATRAKCHI: Aisar Atrakchi. I'm a
16 pharmacology supervisor, Division of Psychiatry.
17 The findings for -- it's a CAD drug, cationic
18 amphiphilic drug, and as you probably know, these
19 drugs cause phospholipidosis by their physical and
20 chemical properties. And it did cause
21 phospholipidosis in animals and as early in two
22 weeks in mice, I believe.

1 So nothing unusual about this. There are a
2 lot of drugs that cause phospholipidosis, and they
3 did cause in this case chronic inflammation. So
4 that's really with longer-term use.

5 In terms of what would be done with it, it's
6 just you remove the drug. The phospholipidosis
7 presumably will go away. But in some of the
8 studies, there was not complete reversal of the
9 phospholipidosis when they removed the drug.
10 Clinically, I can't answer that for.

11 MS. ELMORE: And you're speaking of
12 pulmonary phospholipidosis, specifically?

13 DR. ATRAKCHI: Phospholipidosis was in
14 multiple tissues and organs.

15 MS. ELMORE: And so the inflammation --

16 DR. ATRAKCHI: The inflammation was in the
17 lungs.

18 MS. ELMORE: Okay.

19 DR. BRENT: Dr. Grieger?

20 DR. GRIEGER: The simple answer is I think
21 they characterized it appropriately, but it is a
22 small study. And if there's a program of

1 heightened postmarketing surveillance that could be
2 incorporated to gather that data more consistently
3 for a period of time after the drug reaches greater
4 usage, I think that would be highly beneficial in a
5 subsequent reevaluation of the safety profile and
6 the need for any boxes or warnings.

7 CAPT ANDREASON: If I could address that
8 question. Thirteen of the 16 serious adverse
9 events were considered not drug related. The
10 adverse event reporting system is voluntary, and
11 people, even if they think it's drug related, often
12 don't send in a report. But they don't send in a
13 report if they don't think it's drug related.

14 Therefore, I don't see the spontaneous
15 adverse event reporting system as being an adequate
16 postmarketing safety tool.

17 DR. GRIEGER: I would agree with that having
18 worked in hospitals and knowing what gets turned in
19 and what doesn't get turned in. But I guess what I
20 was suggesting, is there a possibility for
21 something that goes just a bit beyond the normal
22 adverse drug reporting for a period of time,

1 something more like the clozapine REMS system where
2 you'd have to report something in once a month on
3 negative outcomes.

4 CAPT ANDREASON: We actually did consider
5 something like this, but we couldn't figure out
6 exactly what to monitor. We don't know that there
7 is a pathophysiologically unifying mechanism, and
8 so we don't know exactly what to tell people to
9 look out for.

10 The serious adverse events and deaths
11 appeared to be commensurate with what you'd expect
12 in a course of the treatment of Parkinson's
13 disease, but what we see is greater numbers. And
14 this is exactly what we see in the Alzheimer's
15 population.

16 So again, postmarketing, unless it's a
17 large, simple controlled trial, we don't think is
18 going to show anything that's going to be useful.

19 DR. TEMPLE: But, Paul, if there were
20 particular concern with some pulmonary fibrosis or
21 something like that, it's not out of the question
22 that a registry of people could be used to identify

1 such people. It won't get all deaths. That needs
2 a controlled trial, but we can certainly think
3 about that. That's not terribly burdensome.

4 CAPT ANDREASON: True, there --

5 DR. TEMPLE: Limiting use to a particular
6 clinic or something like that, that's a very
7 burdensome thing. People were not entirely happy
8 about clozapine, but a registry of a thousand
9 people to see if there's a pulmonary thing, that's
10 not out of the question.

11 DR. BRENT: Dr. Gerhard?

12 DR. GERHARD: So I started out with a
13 question, and it became even more to the point, I
14 guess. Initially, I just wanted to ask the
15 question what "adequately characterized" in this
16 context means, whether it means adequately to meet
17 requirements for approval, which I believe is what
18 it would mean because obviously, as was stated
19 earlier, we never know enough about the safety of a
20 drug from clinical trials, certainly not from
21 fairly small clinical trials when compared to other
22 indications here.

1 Given the question, though, of what should
2 be done to -- even if this is adequate for approval
3 going forward -- better characterize it and better
4 quantify the risks associated with the treatment,
5 which I think is necessary, I would agree that
6 postmarketing observational research is very
7 limited here because we're looking at a very
8 severely -- an elderly population with severe
9 medical problems that occur, whether or not
10 patients are treated, just at somewhat different
11 rates.

12 To quantify this correctly, certainly with
13 adverse events reporting, is impossible, probably
14 even -- and the details would have to be discussed
15 with observational studies or things like Sentinel.
16 You need some kind of large simple trial. And I
17 think for some of the outcomes like mortality, it
18 should be something that's doable. And I think
19 would think it's something that should be
20 considered as a postmarketing requirement.

21 I don't know whether the comparator here
22 would be placebo or whether the comparator should

1 be something like quetiapine in this context. I
2 don't know enough about the specifics. But in
3 order to better quantify the safety issues, and
4 particularly in the context of whether the safety
5 concerns for severe adverse effects potentially are
6 larger than in the second general antipsychotics,
7 I'm not sure that -- we clearly don't know. The
8 confidence intervals are very wide. Everything to
9 me would point that they're similar, but it would
10 be good to know that they're not of greater
11 magnitude.

12 MS. ELMORE: I'm Susan Elmore. I just want
13 to touch on a couple of points that have been
14 brought up. As a veterinarian toxicologic
15 pathologist, I am concerned about the animal
16 studies. And one thing about the lung is that if
17 we're seeing chronic inflammation in those patients
18 that are treated longer with this drug, that can,
19 as we've seen in the animals, result in fibrosis,
20 which is irreversible once treatment has stopped.
21 So that is of concern, would that also happen in
22 patients treated with the drug.

1 So I think that this postmarket evaluation
2 is important, and the other significant animal
3 lesion was renal disease. I think that that's why
4 I had that original question, was there specific
5 monitoring of pulmonary and renal disease in any of
6 these patients?

7 So that didn't happen, but I think that
8 going forward, that would be something to consider.

9 DR. DUDA: As I recall, it wasn't presented
10 this morning, but I thought there was data
11 regarding the dosing equivalence of the animal
12 studies compared to the human dose.

13 Can the sponsor comment on that?

14 DR. OWEN: To answer the dosing equivalence
15 and others, I invited Dr. Wolfgang, please.

16 DR. WOLFGANG: Grushenka Wolfgang. I'm a
17 toxicology consultant for Acadia. I've been paid
18 for my time to attend the meeting, but I have no
19 financial interest.

20 So in terms of the question about,
21 essentially, is there a safety margin. For the
22 initiation of the event of the phospholipidosis,

1 there's a 5-fold safety margin. For the chronic
2 inflammation, it's a similar margin.

3 I will point out that this was a high-dose
4 lesion. It occurred in the rats at a dose that was
5 above the maximal tolerated dose. And also, in our
6 lifetime -- in the rat carcinogenicity study, where
7 we were just below that maximum tolerated dose,
8 there was no incidence of lung fibrosis, although
9 we did have the phospholipidosis. That was one
10 finding that consistent across the studies.

11 The other important point about this finding
12 is that it's histologically distinct from what you
13 would expect in a diffuse human lung fibrosis. So
14 that's important. And I think lastly what's
15 important is the dose-limiting toxicities that were
16 seen in the early clinical trials. We probably
17 could not reach an exposure level in humans that we
18 could reach in these animal studies to produce that
19 effect.

20 DR. OWEN: And for additional comment,
21 Dr. Stankovic.

22 DR. STANKOVIC: I would like just, if I may,

1 to add regarding the further studies to assess the
2 risks in this respect. We're already planning, as
3 Dr. Demos mentioned earlier, an observational study
4 on 50 sites in 750 patients to follow up for a
5 period of three years. It would be including the
6 patients on all types of treatment for Parkinson's
7 disease psychosis, including pimavanserin if it
8 gets approved.

9 So that's already in plan to follow up the
10 patients. We will be collecting more
11 systematically AEs and SAEs, AEs of interest and
12 SAEs, as well as quality of life and productivity
13 data and caregiver burden. I just wanted to point
14 out that.

15 DR. BRENT: Dr. Elmore, you had a comment.

16 MS. ELMORE: Yes. I was just going to
17 comment that also the FDA stated earlier that there
18 was inflammation, pulmonary inflammation seen in
19 patients who had been treated long-term.

20 I'm sorry. Did you say that?

21 DR. FARCHIONE: Animals.

22 MS. ELMORE: Oh, in the animals, only in the

1 animals but not in people, no evidence of that.

2 Well, I think that what we've seen so far is
3 that based on the studies as they've been done, we
4 haven't seen any evidence that the animal studies
5 translate to humans, and that's a really good
6 thing. I think that's very promising, but I still
7 think that it's something you'd want to keep in
8 mind and consider going forward.

9 MS. BHATT: Before we go on to the question,
10 we read the question again and vote, I'd like to
11 remind everybody to please state your name for the
12 record. It's important that we have your name for
13 the record. Thank you.

14 DR. BRENT: I'm going to read the question.
15 Has the applicant adequately characterized the
16 safety profile of pimavanserin?

17 So I'm also going to read the procedures
18 again. Please press the button on your microphone
19 that corresponds to your vote. You will have
20 approximately 20 seconds to vote. Please press the
21 button firmly. After you've made your selection,
22 the light may continue to flash.

1 If you're uncertain of your vote or you wish
2 to change your vote, please press the corresponding
3 button again before the vote is closed.

4 (Vote taken.)

5 MS. BHATT: The voting results for
6 question 2 is yes, 11; no, 3; abstain, zero; and no
7 voting, zero.

8 DR. BRENT: So we'll go around the room, and
9 everybody can say what they voted and why.
10 Dr. Elmore?

11 MS. ELMORE: Susan Elmore. I voted yes, and
12 just for the reasons already stated. I feel that
13 they've done an adequate job.

14 DR. SARKAR: Urmimala Sarkar. I voted yes.
15 I was particularly convinced by the accumulated
16 safety data from all four of their trials.

17 DR. GERHARD: Tobias Gerhard. I voted yes.
18 Although I have quite a few concerns about the
19 safety data, I think it's sufficient to move
20 forward given the context of the drug as a whole.

21 But as I stated before, I think there would
22 be significant postmarketing commitment advisable

1 to clarify the safety concerns, and I think
2 observational methods are probably insufficient to
3 do that. So some kind of simple trial for some of
4 the severe effects and obviously a robust
5 observational postmarketing program would be
6 important.

7 DR. WINTERSTEIN: Almut Winterstein. I
8 voted no for the exact reason. If they were
9 adequately described, then we would not really come
10 to the conclusion that a phase 4 commitment is
11 needed. I think the data that are here require a
12 phase 4 commitment. There is a statistically
13 significant difference between the two treatment
14 groups when serious adverse events are considered,
15 and that looks too similar to what we have seen in
16 the dementia population to not take seriously.

17 I agree with Dr. Gerhard that observational
18 designs will be difficult in this framework, so a
19 controlled trial, a phase 4 controlled trial, would
20 clearly be the most adequate way to address this.

21 Given the large background incidence of
22 mortality or serious adverse events, that wouldn't

1 require too many patients. And it would certainly
2 allow those patients who are considering those
3 medications to make an informed decision about
4 risk/benefit, which I think right now, we clearly
5 see with the discussions on numbers needed to treat
6 and numbers needed to harm has still a very wide
7 range. And whether a patient is willing to take
8 the risk for a chance of death that is 1 in 10 or 1
9 in 100, to trade in hallucinations, this makes a
10 huge difference.

11 So I think it's very important to have more
12 data to allow everybody to make those decisions.

13 MS. MORGAN: I'm Linda Morgan, and I voted
14 yes. And I am a patient, as you mentioned, and I
15 would give the safety -- I mean, I voted yes, but
16 with hesitation. I don't think it's black and
17 white. And I think we need to take more data,
18 consider more data long-term.

19 DR. SCHMID: Chris Schmid, and I voted no.
20 I feel the numbers here are just really too small
21 to make conclusions. As I raised the issue with
22 the subgroups, I really don't know whether the

1 risks are higher in one group than another based on
2 baseline severity. The death rate is fairly high
3 in this group to begin with, but I don't know if
4 it'd be elevated.

5 So the question asked whether I thought it
6 had been characterized effectively, I just don't
7 think I have enough information to make a decision.

8 DR. GRIEGER: Tom Grieger, and I voted yes
9 to the question posed. I think we'll have more
10 discussion when we get to the discussion of the
11 risks versus benefits. I think they answered the
12 question within the parameters of the protocol, the
13 number of the patients they had in the study, the
14 duration of time that they followed them.

15 MS. WITCZAK: Kim Witczak. I voted no, and
16 I think it's back to the amount of data that we
17 have.

18 DR. PICKAR: I voted yes, but I was
19 concerned about the amount of data. It certainly
20 was going through my mind, but I voted yes.

21 DR. BRENT: David Brent. I voted yes
22 because I thought they adequately characterized the

1 safety and the numbers that they had. The numbers
2 are small. I don't know going forward, if this
3 ends up being approved, whether we need to indicate
4 that there's a higher rate of serious adverse
5 events in the drug than placebo.

6 To me, I'm voting yes because I thought they
7 characterized it, but I think that that's something
8 that should be part of the information that the
9 public has in making their decision.

10 DR. IONESCU: Dawn Ionescu. I voted yes for
11 very similar reasons to Dr. Brent and Grieger.

12 DR. NARENDRAN: Raj Narendran. I voted yes.
13 I was skeptical, but I thought the FDA presentation
14 of antipsychotics in dementia was very illuminating
15 and felt like it wasn't any worse than the existing
16 medications these patients are being put on. But
17 there are some issues that need to be addressed
18 going forward.

19 DR. FAHN: Stan Fahn. I did vote yes also,
20 and I thought they looked at the key important side
21 effect for this class of drugs, the antipsychotics.
22 Does it worsen Parkinson's disease? I think they

1 did a good job looking at that. They didn't show
2 any worsening. That was important.

3 Then, of course, they looked at all the
4 other standard side effects, and I thought they
5 covered everything pretty well. So I thought it
6 was fairly adequate.

7 DR. DUDA: John Duda. I voted yes for
8 similar reasons to Dr. Grieger. I thought given
9 the patients that were exposed -- and keeping in
10 mind that they presented the data for all the
11 studies, not just the definitive of 020 trial, so I
12 thought it was adequate.

13 DR. BRENT: I'm now going to summarize. Our
14 group, the majority of us voted to indicate that
15 the safety characterization was adequate. I think
16 many of us were concerned about the small number,
17 and that caused some of us to vote against that.

18 I think there was a strong endorsement that
19 there should be some kind of postmarketing to try
20 to determine the safety, especially compared to
21 other agents that might be used for this condition.

22 I agree with Dr. Schmid that it looks like

1 there's a difference in the signal between
2 different subgroups. The group with some evidence
3 of dementia actually looked like the rate of
4 serious adverse events was similar between drug and
5 placebo and that that does need to be characterized
6 better.

7 DR. TEMPLE: Can I just ask for a follow-up?
8 There was something like 1200 patients exposed,
9 which is not an untypical number. Is the concern
10 people have that it wasn't long enough, that it
11 wasn't controlled?

12 I heard some reference to the possibility of
13 doing what I take to be a large long-term
14 controlled trial in presumably these people. And
15 I'd be interested in hearing whether people think
16 that's a realistic possibility. It's not easy for
17 me to imagine people in this condition entering
18 such a trial against placebo. And entering it
19 against another active drug will be uninformative,
20 so that's not going to be very helpful.

21 So a little bit of discussion, I don't want
22 to take hours, but a little discussion of this

1 would be helpful to us.

2 DR. BRENT: Dr. Grieger?

3 DR. GRIEGER: I think it's a great question.
4 I mean, they did follow a large number of people in
5 one way or another over time, but many of them
6 weren't controlled. It was open label at that
7 point in time. I don't know how tight the
8 reporting was during that period of time.

9 Quite frankly, to the extent they reported
10 it, it kind of glossed right over me compared to
11 the data where they looked specifically at the
12 placebo and the trial group and the control group
13 during a specific period of time and reported the
14 events.

15 So I think it's just a matter of the
16 open-label component of that did not seem quite as
17 rigorous. And I agree. I mean --

18 DR. TEMPLE: But it's not an accident the
19 controlled trial only went 6 weeks. I doubt people
20 would be willing be in for much longer, so then
21 they crossed over to active drug because --

22 DR. GRIEGER: Right. But the other issue is

1 depending on the age of these people, looking at
2 Medicare beneficiaries, something like two-thirds
3 of them end up dying in a six-year period of time
4 once they enter into the registry. So there is an
5 issue with long-term trials in patients who have,
6 for some of them, a very serious, potentially fatal
7 disease of itself.

8 DR. BRENT: Dr. Winterstein?

9 DR. WINTERSTEIN: If I recall the numbers,
10 there were roughly about 20 or 25 percent of
11 patients who were on treatment, on other
12 antipsychotic treatment, at study entry, so there
13 was a fairly large population of patients who were
14 not treated at study entry and who had had
15 psychotic symptoms for a range of time.

16 So it doesn't seem that every single patient
17 requires treatment immediately or makes a decision
18 to get treated immediately.

19 DR. TEMPLE: Maybe you could do a comparator
20 trial, but would that get you the answer you want
21 to know? We already believe those drugs cause all
22 kinds of problems, as the data you've seen already

1 shows. So if you did this and they were similar,
2 what would you conclude? I don't know. It sounds
3 like you really need a placebo or a no-treatment
4 group.

5 Anyway, thanks for the discussion, though.

6 DR. BRENT: Dr. Sarkar?

7 DR. GERHARD: This is Toby Gerhard. I think
8 it would still be important to see that this drug
9 is not worse, which we certainly can't rule out.
10 If we have an active comparator, given the
11 background rates, I don't think it would have to be
12 a long-term trial, and I don't think it would have
13 to be a tightly controlled trial.

14 So a simple trial with a mortality outcome
15 assessed after a relatively short period could be
16 even 6 weeks, done in -- again, it could be an easy
17 power calculation, but a thousand patients or so
18 may be something that's doable and would be
19 informative, for example, even against placebo for
20 a short period or compared to quetiapine, which
21 might be the most comparable.

22 I think that would be informative and would

1 certainly help us quantify the mortality risk that
2 we're talking about. For some of the other
3 obviously severe adverse effects, it becomes much
4 more difficult because the outcomes assessment is
5 so much harder.

6 DR. BRENT: Dr. Sarkar?

7 DR. SARKAR: I hope I don't get booted out
8 the door for saying this, but I think a well-done
9 observational study would actually add a lot.
10 People are going to be using these drugs in the
11 real world in a lot of different ways, and I think
12 having some information about serious adverse
13 effects and mortality just with real-world use in a
14 larger, more diverse patient group would be very
15 helpful.

16 DR. BRENT: Dr. Schmid?

17 DR. SCHMID: Yes, I would agree. I'm not
18 even sure you need a placebo group here. I'm just
19 looking at the data. Really, what was presented
20 was there were 433 people in the 34-milligram group
21 and the placebo group, and there's 3 deaths out of
22 124 in the 34-milligram group.

1 So that's about a 2 and a half percent death
2 rate. And I just would like to know -- that's
3 3 times greater than what's in the placebo group.
4 We all know what's happened with drugs that have
5 gone on the market and then had to be pulled
6 because the death rate goes up by 20 percent.
7 We're talking about a 200 percent increase here
8 potentially. I agree it's only 4 people.

9 So that was why I voted no because I just
10 don't know whether that's real or not.

11 DR. BRENT: Thank you.

12 The third question is whether the benefits
13 of pimavanserin for the treatment of psychosis
14 outweigh the risk of treatment. Basically, the
15 risk/benefit ratio. So we'll have discussion about
16 that.

17 DR. GRIEGER: I think it would be helpful to
18 perhaps categorize the patients that a physician
19 would select for this medication, whether it
20 includes using the SAPS-PD with a baseline score,
21 or number of symptoms, or key symptom with a
22 severity rating on it; not as a prescriptive

1 measure, but to just put that into the prescription
2 guideline so that it isn't just a drug that you
3 pull off the shelf when you pull the other ones off
4 to give it a try.

5 I mean, it really should be people with a
6 serious enough problem that you're willing to
7 introduce a potential risk of an adverse event. I
8 mean, we're supposed to do that all the time, but
9 if you get people in primary care that are just
10 throwing meds at something -- not to malign primary
11 care, but there are people who sometimes prescribe
12 these medications who have less experience with the
13 subtleties of these medications and the long-term
14 implications.

15 DR. DUDA: Just out of curiosity to the FDA,
16 is there any precedent for a black box warning upon
17 approval?

18 CAPT ANDREASON: Yes.

19 DR. DUDA: Sounds like a good option to me.
20 I mean, honestly, that would take care of that
21 problem.

22 DR. PICKAR: What would you suggest the

1 black box would say? How would you take a crack at
2 that, John?

3 DR. DUDA: Oh, boy.

4 DR. PICKAR: Because I think it's an
5 interesting thought.

6 DR. DUDA: I guess it would be similar to
7 the black box warning for atypicals in dementia,
8 suggesting that there's an increased risk of
9 mortality.

10 DR. TEMPLE: Well, a question that we have
11 to decide on -- and to my best knowledge, it has
12 not been decided -- is whether the class box
13 warning, which is given to all of them, whatever
14 their particular nature, should also be applied to
15 this. And I don't think we've decided that yet.

16 DR. BRENT: Dr. Sarkar?

17 DR. SARKAR: The way clinicians use black
18 box warnings in the real world, at least for me as
19 a clinician, I don't feel like I have enough data
20 to say this needs -- I mean, the numbers are so
21 tiny. It's just -- it doesn't feel meaningful
22 enough to make such a large psychological barrier

1 for a clinician prescribing it. That's why I think
2 we need more information.

3 DR. FAHN: Stan Fahn, and I just agree with
4 you completely. I think it's still too small, and
5 you need a longer surveillance period to see if
6 this really holds up or not. I mean, as somebody
7 mentioned earlier in the discussions this morning,
8 that a one-number change would have made a big
9 difference.

10 One other thing about this question, I
11 pointed out earlier that there are some side
12 effects that were more common in the placebo group
13 than in the active drug treatment group. Are these
14 flukes, or could there be something in this drug
15 that has some benefits that we didn't know about in
16 advance and it needs to be explored?

17 But I put that into the equation. Does the
18 treatment with this drug outweigh the risks of side
19 effects? And I think maybe this has to be put in
20 the equation on the positive side as well. So keep
21 that in mind when I look at this.

22 DR. BRENT: Ms. Witczak.

1 MS. WITCZAK: This is regarding the black
2 box warning. I do think as a consumer that if it's
3 a class-wide -- because if this does not have a
4 black box warning on it, I can see it being out
5 there and being promoted by the doctors that this
6 might be another type of drug that does not have
7 any of the side effects.

8 So I don't think it really adequately
9 explains it because there are deaths that are
10 associated, whether we have enough data or not.
11 But if it's a class-wide, I think it's something to
12 consider.

13 DR. BRENT: I just wanted speak to
14 Ms. Witczak's comment, which is if you voted that
15 there was enough data to determine the safety
16 profile, then we have enough data to decide whether
17 or not there should be a warning. If we're saying
18 that we don't -- and we already voted. But to me,
19 I feel like I voted at least to say that there was
20 enough data to characterize the safety. But there
21 is a signal that there are more serious adverse
22 events and death in the group that got the drug,

1 and I think that that should be passed on to the
2 consumer.

3 DR. TEMPLE: There is some class language
4 that is not based on the data from the new
5 submission. So antidepressants all say something
6 about suicidality, antiepileptic drugs do, and it
7 isn't because you have data for each new drug that
8 confirms that. To me, the idea that 3 versus 1
9 somehow confirms the mortality finding is really at
10 the outer edge.

11 But we do sometimes continue the class
12 warnings. A new antipsychotic, for example, for
13 conventional treatment, would ordinarily get the
14 same box that all the rest of them do because of
15 the accumulated data on the whole class, not
16 because of in their trials they showed this, which
17 they almost never would.

18 So anyway, we haven't decided on that, but
19 we're going to think about that.

20 DR. BRENT: Dr. Duda?

21 DR. STONE: Yes. I didn't go into this in
22 the talk, but all those drugs were these, except

1 for haloperidol, atypical antipsychotics. And
2 haloperidol, while it still had very similar
3 mortality rate, relative risk, the deaths in the
4 haloperidol group were different. They were things
5 like cancer, things that you would expect would be
6 due to chance rather than something going on with
7 the drug.

8 But we nonetheless decided to extend the
9 warning to all the antipsychotics, not just the
10 atypicals or second generation, in part, because we
11 didn't want to imply that they were necessarily any
12 safer.

13 Bob's right. If you have 3 deaths versus 1
14 here, it doesn't matter very much. You have a
15 prior based on your -- and what we know about the
16 antipsychotics, that 3 versus 1 is going to move
17 that prior only very slightly. So it's still
18 basically how relevant you think that our
19 experience with these other antipsychotics in
20 demented patients is to this drug.

21 DR. BRENT: Dr. Grieger?

22 DR. GRIEGER: I think it raised a very

1 interesting question. Are you going to classify
2 this as an antipsychotic? My recommendation would
3 be not because to class -- this goes back to what
4 Dr. Pickar was saying earlier. If people view this
5 as an antipsychotic, then it's free rein to use it
6 on schizophrenia, bipolar with psychosis,
7 depression with psychosis.

8 I wouldn't characterize it that way. It
9 hasn't been proven that way. In fact, I think it's
10 been looked at that way, and it's now being looked
11 at a very specific way. So I think it's a unique
12 drug, which may carry some of the risks of the
13 other drugs, but it acts by a pretty different
14 mechanism, a novel mechanism. And it's for a very
15 novel population of people. That's all that it's
16 been proven to work with. So I wouldn't class it
17 as an antipsychotic because I think it would
18 escalate the chance for misuse in the professional
19 community.

20 I guess what I was getting at is something
21 similar to -- and it wouldn't have to be, again,
22 prescribed or proscribed if you didn't do it, but

1 something that says this drug has been proven to be
2 effective in patients that are like this, this,
3 this, and this, so that it just kind of lays out
4 what is the population that you'd want to use this
5 drug in: well, they've had Parkinson's disease for
6 at least a year; well, they've had hallucinations
7 for at least a month; well, these hallucinations
8 are causing some kind of an impairment for them.

9 Whatever you-all work out with regard to the
10 words, it should match what the study has been
11 about, what kind of patients in what kind of
12 setting.

13 DR. PICKAR: No surprise, I would agree with
14 Tom on that part. The idea of labeling it an
15 antipsychotic and that we're putting it in the
16 category of those others, I think is a problem and
17 hopefully not necessary.

18 It goes back to my earlier point about
19 psychosis in drug-treated Parkinson's disease.
20 It's a very specific thing with a very limited
21 amount of data that we've seen. And I would have
22 loved to have seen other data. It didn't show it

1 from other trials. So with this, I don't think it
2 should be in that broad category.

3 DR. TEMPLE: Well, this has been very
4 helpful, but we don't have to label it an
5 antipsychotic to believe that the concern from
6 those other drugs still applies. So those are
7 somewhat separate questions, and we'll take all
8 this into account.

9 Just to state the obvious, section 14, which
10 describes the trials, is very good at giving who
11 exactly was in the trials. Elements of that may or
12 may not appear in the indication section. We don't
13 like to make them too crowded. But that's a
14 determination that's going to have to be made.

15 DR. SCHMID: I just had a point of
16 clarification, back to the Mini-Mental. What
17 percentage of the people were in those two groups?
18 I don't recall whether you had those numbers.

19 DR. STANKOVIC: We'll bring that slide right
20 up. There were about 50 people in the group that
21 it was lower. Slide up, please.

22 There was in lower, yes, category of

1 Mini-Mental Status Exam versus 135 in the other.

2 DR. SCHMID: And this is in both studies?

3 DR. STANKOVIC: This is study 020, just the
4 pivotal trial, yes.

5 DR. SCHMID: Okay. So the numbers you
6 showed before, I think there were 12 serious
7 adverse events -- greater than 25?

8 DR. STANKOVIC: We can project that again,
9 yes.

10 DR. SCHMID: I'm just trying to figure out
11 what the rate of --

12 DR. STANKOVIC: These numbers are very
13 small, so it's --

14 DR. SCHMID: I know. I know. I'm just
15 trying to figure out what the rate of adverse
16 events was in that group.

17 DR. STANKOVIC: Slide up, please. So we had
18 in patients of less than 25, we had 4 and 3 events
19 in pimavanserin and placebo arm versus 8.5 versus
20 2.9 percent in pimavanserin versus placebo in
21 patients with a Mini-Mental Status Exam above 25.

22 DR. SCHMID: So it's higher, but I agree the

1 numbers are small, so you don't really know if
2 those are differences. Okay.

3 DR. STANKOVIC: Right, right.

4 DR. SCHMID: Thanks.

5 DR. BRENT: I'm going to re-read the third
6 question. Do the benefits of pimavanserin for the
7 treatment of psychosis outweigh -- wait a
8 minute -- associated with Parkinson's disease
9 outweigh the risk of treatment?

10 DR. TEMPLE: Associated with treated
11 Parkinson's disease. I'm just trying to satisfy
12 you.

13 DR. BRENT: Okay.

14 DR. DUDA: Sorry. John Duda. One last
15 question. Can you give us some guidance on how the
16 characterization of breakthrough therapy
17 designation should impact this consideration of
18 this question?

19 DR. FARCHIONE: I think that the issue of
20 the breakthrough therapy, it's something that we
21 assign to the development program. So it helps to
22 get to this stage where we're talking about the

1 actual drug application more efficiently, sooner,
2 whatever. But as far as the choice of whether the
3 benefits outweigh the risks, it's the same as it
4 would be for anything else.

5 DR. BRENT: Everyone vote now.

6 (Vote taken.)

7 MS. BHATT: The voting results, yes is 12;
8 no is 2; abstain is zero; no voting is zero. And
9 we'll go around the room, starting with Dr. Duda
10 first. Please state your name for the record and
11 why you voted.

12 DR. DUDA: John Duda. I voted yes for many
13 of the comments I made before. I thought that
14 given the -- it was proven effective, and the side
15 effect profile, while somewhat concerning, is not
16 convincing to me that it will stand up in larger
17 numbers.

18 I think that from a movement disorder
19 clinician perspective, I have plenty of patients
20 who would tell me that they would gladly take a
21 medication if they had moderate to severe psychosis
22 in Parkinson's disease that had a 1 in 10 chance of

1 completely resolving their symptoms and if it had a
2 1 in 100 chance of killing them. They would still
3 be happy to take it.

4 DR. FAHN: Stan Fahn. I voted yes. I think
5 although the benefit is not as great as I would
6 have liked, it's got some benefit. I think it may
7 help a number of our patients, and we need
8 something. This is a real big problem, and
9 therefore, I voted yes.

10 I think the side effects presented don't
11 outweigh the benefit, and the benefit outweighs the
12 side effects. And that's why I voted yes.

13 DR. NARENDRAN: Raj Narendran. I voted yes
14 for the above stated reasons.

15 DR. IONESCU: Dawn Ionescu. I voted yes as
16 well. I just think especially for these disorders
17 that are really difficult to treat where we have no
18 options, many of these patients will say yes, I'm
19 willing to take the risk. And I think, obviously,
20 this question is going to need to be discussed with
21 every patient that's started on this type of
22 medication. But nonetheless, giving them something

1 that may help them for their severe disease is
2 going to outweigh the risks for many of them.

3 DR. BRENT: David Brent. I also voted yes
4 and for the same reasons. I was persuaded actually
5 by the really terrible quality of life that these
6 patients have. And I think as long as they can be
7 given an informed choice about the risks, I think
8 they ought to have the options.

9 DR. PICKAR: I voted yes as well. My
10 concerns were already established, and Bob
11 addressed them. And I'm just very pleased that
12 we're going to hopefully help something get
13 into -- treatment to help some of you folks out
14 there and others folks who need it.

15 I think the concern around safety is real,
16 and everyone is trying to do -- both to help people
17 just to make sure that no one gets hurt by this.
18 So I'm a yes.

19 MS. WITCZAK: Kim Witczak, no. And I'm for
20 patients having treatments that are really
21 beneficial that doesn't -- at the expense of
22 safety. I'm not convinced with this one. I think

1 patients need to have all the information, and I'm
2 just really concerned.

3 I'm in advertising. It's my background.
4 I'm really concerned about how this is going to
5 eventually going to get promoted into the PR, into
6 the community. And I'm afraid of the other
7 populations that will start using it off label.

8 DR. GRIEGER: Tom Grieger. I voted yes for
9 the reasons already outlined by others.

10 DR. SCHMID: Chris Schmid. I voted yes with
11 some reservations. I think the need here outweighs
12 the potential risk, which I really, as I voted no,
13 can't even characterize that. So I guess I'm
14 hoping that the risks are going to be small, and I
15 think the benefits for some of these people who are
16 very sick and whose families are affected by this,
17 I think they're probably willing to take that risk.

18 MS. MORGAN: Linda Morgan. I voted no
19 because of all the discussion of this.

20 DR. WINTERSTEIN: Almut Winterstein. I
21 voted yes. If there were a safe and effective
22 alternative on the market, I would not have voted

1 yes. But I think that, in particular, the public
2 hearing today was very compelling. There clearly
3 is a need.

4 I agree with Dr. Brent that patients need to
5 be able to make an informed decision. I think
6 right now with the data they have, they cannot. So
7 I would very much recommend that the FDA does
8 consider a phase 4 study to allow patients to make
9 that decision.

10 DR. GERHARD: Tobias Gerhard. I voted yes
11 as well for the reasons that were stated before.
12 Definitely have some concerns about the safety. I
13 think it is generally a slippery slope to compare
14 the harms of a medication to be approved for a
15 condition where there aren't a lot of alternatives,
16 or any alternatives, with unapproved alternatives
17 that people use.

18 But I think in this situation, it is
19 somewhat justified because, clearly, the
20 antipsychotics and the second generation
21 antipsychotics are used very widely. And clearly,
22 it is, in my perception, almost standard of

1 practice to do so.

2 So in that sense, I think there is merit to
3 make that comparison to that class of drugs that
4 clearly comes with its own established safety
5 concerns. So in that context, I think it's a yes,
6 though we need a robust postmarketing program for
7 this drug.

8 DR. SARKAR: Urmimala Sarkar, I voted yes
9 with the plea to the FDA to please consider a large
10 observational study so we can ensure that once it
11 goes into real-world use, that the benefits will
12 outweigh the risks.

13 MS. ELMORE: I'm Susan Elmore. I voted yes,
14 and I don't think that this drug is the golden egg
15 for Parkinson's disease psychosis. There are
16 certainly some risks in terms of SAEs and even
17 death. But importantly to me, in this study, there
18 were no underlying mechanisms, no unifying
19 mechanisms that could link them all. And that was
20 important to me.

21 Also importantly is that it does not worsen
22 the symptoms of Parkinson's disease. And

1 obviously, we've already stated, no currently
2 available effective treatment for Parkinson's
3 disease psychosis that won't block dopamine
4 receptors.

5 So for me, there was a clear need for such a
6 drug, and the benefits did outweigh the risks for
7 this particular group of patients.

8 DR. BRENT: So I will summarize now. I
9 would say that even the people that voted yes did
10 so with qualifications. There's concerns about the
11 safety and emphasis that the FDA should be as
12 specific as possible in the labeling of the drug,
13 that to try and do what we can to prescript
14 off-label use.

15 But given the lack of alternatives and the
16 poor quality of life of this condition, I think
17 that explained the majority of people endorsing the
18 favorable risk/benefit ratio.

19 I have one last thing to read, or two last
20 things. Before we adjourn, are there any last
21 comments from the FDA?

22 DR. UNGER: Thanks. I'm Ellis Unger. I'm

1 director of Office of Drug Evaluation I.

2 One of the issues, one of the places I had
3 hoped someone would go, but no one went there, is
4 that in the evaluation of benefit and risk, one of
5 the critically important aspects is whether an
6 individual patient can figure out if they're
7 deriving benefit from the drug that they're taking.

8 So sometimes if we put a stent in somebody's
9 coronary arteries, we say here, take this
10 anti-platelet drug for the rest of your life. Good
11 luck. The patient just takes it and is subjected
12 to whatever the risk is.

13 My question is whether an individual patient
14 who has psychosis associated with Parkinson's
15 disease could take the drug and figure out that
16 they're feeling better, that they're having fewer
17 hallucinations, less problem, and continue the
18 drug; whereas the person who feels like I'm not
19 really feeling any better would know that, because
20 if they know that, they can stop the drug. And
21 that really enhances the benefit/risk relationship
22 of the drug.

1 So for the people around the room who treat
2 patients with this disease, I'm just wondering if
3 they think an individual patient can figure out if
4 they are feeling better if they're taking the drug.

5 DR. DUDA: John Duda. Certainly, from my
6 experience with the other atypical antipsychotics,
7 that's the case. We often start out at a very low
8 dose of quetiapine, for example, and ask the
9 patient, and maybe importantly, the caregiver, if
10 they see a difference in behavior. And often, they
11 do. Sometimes they don't, in which case we kind of
12 titrate the dose effectively.

13 So it is possible based on patient and
14 caregiver personal perspective of the efficacy to
15 even titrate the dose. Obviously, this won't have
16 a dose titration, I guess, but we use that
17 clinically.

18 DR. FAHN: Stan Fahn. Let me also add to
19 that that let's say we did add a little bit of
20 quetiapine, and the drug works, they're better.
21 And for a period of time, maybe six months, a year
22 or so, everybody is fine, we would talk with the

1 patient and the caregiver and with the physician,
2 of course, and we'd discuss how about coming off
3 and see how they do. And that's very common.

4 So we do that, and if they have symptoms
5 again, we reintroduce it.

6 DR. UNGER: Ellis Unger again. So still,
7 something we sometimes put on the label, reassess
8 how well you think the patient is doing and
9 reassess the need for the drug. And maybe that
10 could help mitigate some of the concerns around the
11 room about the safety. I see people shaking heads.

12 DR. BRENT: Ms. Witczak?

13 MS. WITCZAK: I was just going to say, how
14 many people -- will it go to the GPs and the
15 internists? Because that's one of the things that
16 I think a lot of times, with a lot of these
17 medications, they do go into the physician thinking
18 that it's themselves and the disease. And
19 physicians are often not able to identify that it's
20 the treatment drug that's causing it.

21 So I think that is a big concern, especially
22 when you get into the GPs.

1 DR. BRENT: Are there any additional
2 comments?

3 DR. GRIEGER: I guess I'd ask the
4 neurologists in the room what -- I mean, from my
5 sense as a psychiatrist, even though I've got some
6 training in neurology, I wouldn't feel comfortable
7 in managing these patients by myself.

8 Do you find general practice, internists,
9 that just feel comfortable adjusting doses without
10 consulting with you-all?

11 DR. FAHN: I think most neurologists get
12 some training from specialist movement disorders
13 during their training program, residency, and also
14 the CME courses. Internists, I think, are
15 uncomfortable once they get any complications from
16 a Parkinson's drug, a little bit dyskinesia is
17 wearing off, and they don't want to touch them
18 anymore, and they send the patients to the
19 neurologists. And many neurologists will send them
20 to a movement disorder specialist because of the
21 same problem.

22 It becomes very sophisticated. I should

1 point out to everybody, Parkinson's disease is a
2 very complex disorder. We already heard about the
3 motor, non-motor, but it's also difficult in the
4 treatment. These drugs do all kinds of
5 things -- the drugs we use to help the patients do
6 all other kinds of problems, and we just discussed
7 one of them today.

8 This is a much more complicated disease than
9 we anticipated, and even the movement disorder
10 specialists are having a hard time getting a grasp
11 on how to best to do. We still don't know when
12 it's best to start levodopa. After all these
13 years, what, 40 years or 50 years of levodopa,
14 should we start right away, should we delay it?
15 This is still an unanswered question.

16 So it's an evolving thing. It's part art,
17 part science. So I think many doctors won't feel
18 comfortable handling this and would send it to a
19 specialist.

20 DR. BRENT: Dr. Sarkar?

21 DR. SARKAR: I'm actually a general
22 internist, and I practice in a setting where there

1 aren't very many subspecialists. But I would say
2 that titrating Parkinson's medications is solidly
3 in the purview of a specialist.

4 **Adjournment**

5 DR. BRENT: If there are no other comments,
6 then I'd first like to thank everybody for their
7 participation, and we'll now adjourn this meeting.

8 Panel members, please take all your personal
9 belongings with you as the room is cleaned at the
10 end of the meeting day. All materials that are
11 left on the table will be disposed of. Please
12 remember to drop off your name badge at the
13 registration table on your way out so they may be
14 recycled. Thanks again.

15 (Whereupon, at 3:49 p.m., the meeting was
16 adjourned.)

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