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

Meeting Roster

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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

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

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

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

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

CAPT ANDREASON: I'm Paul Andreason. I am

the clinical reviewer for this NDA.

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

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

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

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

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

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

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

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

professor of psychiatry at Uniformed Services University.

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

MS. MORGAN: Linda Morgan, patient.

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

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

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

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

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

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

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

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

meeting topic during breaks or lunch. Thank you.

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

Conflict of Interest Statement

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

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

interest laws.

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

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

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

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

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

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

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

employed by Boehringer Ingelheim.

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

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

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

FDA Opening Remarks

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

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

Now, about the drug, pimavanserin is, in terms of its pharmacology, a 5-HT2A inverse agonist, which is different than the usual atypical antipsychotics. But because we as psychiatrists tend to name new groups of drugs as being not the old group of drugs, we had typical antipsychotics and then atypical antipsychotics, this drug at least for now is an atypical antipsychotic, but its pharmacology is different than the other drugs.

As a 5-HT2A inverse agonist without dopaminergic activity, it's a drug that was used by the sponsor to put into patients who need their dopamine activity for the other parts of their disease to be treated. So it makes some pharmacologic logical sense to have a drug with a different mechanism of action for this disease.

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

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

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

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

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

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

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

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

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

DR. BRENT: Both the FDA and the public believe in a transparent process for the information-gathering and decision-making. To ensure such transparency at 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 all participants, including the sponsor's nonemployee presenters, to advise the committee of any financial relationships that they may have with the firm at issue, such as consulting fees, travel expenses, honoraria, and interest in the sponsor, including equity interest and those based upon the outcome of the meeting.

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

We will now proceed with the applicant's presentations.

Applicant Presentation - Michael Monahan

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

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

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

The recommended dose of pimavanserin is 34 milligrams taken orally as two 17-milligram tablets once daily. Pimavanserin offers a novel approach to the treatment of psychosis. It is a highly selective and potent serotonin inverse agonist with pharmacological activity driven through its blockade of 5-HT2A receptors.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Applicant Presentation - Stuart Isaacson

DR. ISAACSON: Thank you.

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

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

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

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

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

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

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

While we've thought over the years that dopaminergic medications can trigger these symptoms, a number of studies have failed to find a clear association between the dose or class of medications. Like most non-motor symptoms, PD psychosis is an inherent part of the underlying synuclein neurodegenerative process, probably involving serotonergic dysfunction with evidence of involvement of 5-HT2A receptors.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

with progressive mobility problems and managing polypharmacy.

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

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

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

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

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

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

Unfortunately, with the lack of effective

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Applicant Presentation - Serge Stankovic

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

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

lower selectivity compared to 5-HT2A. The biological rationale for utility of 5-HT2A inverse agonist for treatment of psychotic symptoms is based on observation that visual hallucinations are associated with excessive 5-HT2A transmission in the areas responsible for visual processing and that the number of 5-HT2A receptors is increased in the sensory cortex of patients experiencing psychotic symptoms.

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

development.

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

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

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

In order to evaluate the long-term safety of

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

placebo group.

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

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

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

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

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

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

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

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

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

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

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

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

Even more striking was the proportion of

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

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

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

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

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

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

the SAPS-PD score.

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

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

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

In study 020, there was significant

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

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

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

I will now show available efficacy data from

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

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

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

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

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

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

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

antipsychotics in schizophrenia, for instance.

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

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

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

were used.

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

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

improved on the CGI-I or Clinical Global Assessment.

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

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

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

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

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

Applicant Presentation - George Demos

DR. DEMOS: Thank you, Dr. Stankovic.

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

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

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

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

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

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

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

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

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

least 5 percent of those subjects.

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

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

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

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

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

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

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

The next subject reported as respiratory distress is an 84-year-old female with history of orthostatic hypotension and depression. Pimavanserin was discontinued about a month after randomization, 4 days prior to her admission for cataract surgery. Postoperatively, she was fatigued and never regained full alertness.

An unspecified elevation of the white blood cells was reported, and she had a fever of 101.8. The following day, she was described as having hypoventilation of the right lung, and she was started on antibiotics and oxygen. Two days later, a chest x-ray revealed left lung atelectasis, and she was intubated. And 2 weeks after that, a tracheotomy was performed. But her respiratory status declined, and she died on day 61, 32 days post her last dose of pimavanserin.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

events.

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

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

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

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

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

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

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

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

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

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

Sixty-two deaths have been reported over the

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

cardiovascular disease.

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

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

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

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

Applicant Presentation - Serge Stankovic

DR. STANKOVIC: I would like to put the

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

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

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

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

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

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

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

requiring dopaminergic therapy.

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

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

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

Modest QT prolongation was observed with

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

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

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

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

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

Applicant Presentation - Clive Ballard

DR. BALLARD: Thank you.

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

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

I am to give a clinical perspective of

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

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

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

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

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

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

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

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

on quality of life for both individuals is absolutely massive.

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

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

Based on a thorough review of randomized

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

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

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

been described, albeit with a small number of events.

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

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

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

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

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

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

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

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

of medicine.

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

Clarifying Questions to Applicant

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

Dr. Fahn?

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

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

different observers looking and asking the questions?

If somebody can please explain that to me.

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

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

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

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

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

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

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

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

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

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

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

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

DR. ISAACSON: Thank you, Dr. Fahn.

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

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

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

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

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

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

DR. BRENT: Dr. Ionescu.

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

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

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

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

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

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

placebo group without serotonin reuptake inhibitors.

DR. BRENT: Dr. Grieger?

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

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

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

DR. OWEN: Dr. Stankovic.

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

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

DR. GRIEGER: Thank you. That answers it.

DR. BRENT: Dr. Winterstein?

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

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

So basically, what we have left is really

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

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

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

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

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

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

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

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

DR. OWEN: Relative to the original.

Dr. Stankovic.

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

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

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

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

is correlated to the CGI clinician assessment.

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

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

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

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

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

DR. BRENT: Dr. Pickar?

DR. PICKAR: Thank you.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

DR. STANKOVIC: Oh, okay.

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

DR. STANKOVIC: Right, right.

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

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

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

DR. STANKOVIC: Yes.

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

had it. And some MAO inhibitors.

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

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

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

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

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

Second question was schizophrenia data,

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

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

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

What is its efficacy in schizophrenia?

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

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

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

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

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

DR. STANKOVIC: We do not have those.

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

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

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

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

DR. PICKAR: Fair enough.

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

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

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

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

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

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

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

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

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

physician, which was clearly hallucinations in the narrative.

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

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

DR. BRENT: Dr. Narendran?

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

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

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

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

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

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

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

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

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

DR. BRENT: Hi. Ms. Witczak?

MS. WITCZAK: Hi. Thank you.

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

that decision? That's the first.

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

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

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

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

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

basically it. I mean, you would --

DR. OWEN: It's the same question?

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

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

Dr. Stankovic.

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

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

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

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

DR. OWEN: Dr. Stankovic.

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

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

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

DR. BRENT: Dr. Gerhard?

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

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

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

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

driven by potential uncontrolled confounding or other biases.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

MS. ELMORE: Or renal.

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

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

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

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

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

minimal as to be clinically insignificant?

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

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

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

DR. BRENT: Dr. Schmid?

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

In slide CS-9, which combines studies 012

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

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

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

Dr. Stankovic.

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

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

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

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

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

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

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

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

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

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

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

discontinuations are becoming more comparable.

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

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

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

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

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

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

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

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

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

also showed that pimavanserin was statistically superior to placebo.

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

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

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

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

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

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

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

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

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

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

the same results.

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

DR. BRENT: Yes.

DR. TEMPLE: You didn't answer that.

DR. STANKOVIC: I'm sorry.

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

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

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

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

DR. BRENT: Thank you.

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

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

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

DR. BRENT: Thank you.

Dr. Duda?

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

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

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

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

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

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

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

These are patients you try to take away some

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

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

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

having more psychosis.

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

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

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

DR. BRENT: Dr. Fahn?

DR. FAHN: Stan Fahn, Columbia University.

I have a couple questions. The first is for

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

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

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

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

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

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

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

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

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

intriguing. Thank you.

DR. BRENT: Dr. Pickar?

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

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

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

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

antipsychotic.

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

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

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

DR. STANKOVIC: Right.

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

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

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

DR. PICKAR: They did better.

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

DR. PICKAR: Right --

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

DR. PICKAR: Right.

DR. BRENT: Did you have an additional comment?

(No response.)

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

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

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

FDA Presentation - Paul Andreason

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

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

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

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

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

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

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

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

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

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

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

The primary endpoint was the nine items of

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

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

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

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

23 percent difference.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

FDA has not approved an antipsychotic drug with this safety signal for use in the agitated, psychotic for demented elderly populations. However, previously when these applications came to us, the drugs that were under review were already on the market. If we follow our usual logic and didn't approve pimavanserin for the treatment of Parkinson's disease psychosis, it couldn't be used off label. It wouldn't be available. So that is our dilemma from a regulatory point of view.

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

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

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

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

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

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

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

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

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

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

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

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

The number of patients who were clinically

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

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

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

and here's the reference for that.

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

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

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

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

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

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

For study 020, the number needed to harm

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

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

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

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

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

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

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

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

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

Questions?

Clarifying Questions to FDA

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

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

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

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

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

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

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

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

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

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

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

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

CAPT ANDREASON: Yes, right.

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

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

DR. PICKAR: Okay.

CAPT ANDREASON: So other questions?

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

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

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

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

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

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

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

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

CAPT ANDREASON: Day-to-day variability.

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

CAPT ANDREASON: Perhaps Acadia can answer that question.

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

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

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

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

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

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

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

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

DR. BRENT: Dr. Winterstein?

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

CAPT ANDREASON: Sure.

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

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

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

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

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

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

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

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

CAPT ANDREASON: Twenty-five?

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

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

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

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

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

DR. WINTERSTEIN: Okay.

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

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

CAPT ANDREASON: Right, these were --

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

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

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

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

DR. BRENT: Dr. Gerhard?

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

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

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

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

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

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

the other antipsychotics.

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

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

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

DR. BRENT: Dr. Grieger?

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

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

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

DR. GRIEGER: Okay.

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

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

CAPT ANDREASON: Correct.

DR. GRIEGER: Okay.

DR. BRENT: Dr. Morgan?

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

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

CAPT ANDREASON: That's correct.

MS. MORGAN: Okay.

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

MS. MORGAN: Right.

CAPT ANDREASON: Correct.

MS. MORGAN: Okay. Thanks.

DR. BRENT: Ms. Witczak?

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

significance with the placebo effect.

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

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

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

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

something that's not otherwise available.

Can I ask a question also of Paul?

DR. BRENT: Sure.

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

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

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

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

DR. TEMPLE: Okay.

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

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

CAPT ANDREASON: Right.

DR. TEMPLE: Okay.

DR. BRENT: Dr. Fahn?

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

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

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

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

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

CAPT ANDREASON: All right.

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

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

serious adverse events that were experienced on drug.

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

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

(No response.)

CAPT ANDREASON: Good. Thank you very much.

FDA Presentation - Marc Stone

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

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

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

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

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

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

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

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

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

I think when we're just looking at these

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

So it is possible that if there had been

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

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

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

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

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

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

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

Clarifying Questions to FDA

DR. BRENT: David Brent. You indexed the

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

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

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

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

appeared to have a somewhat better effect.

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

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

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

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

DR. BRENT: Thank you.

Dr. Schmid?

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

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

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

Slide up. In terms of your --

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

DR. STANKOVIC: Right.

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

DR. STANKOVIC: Right.

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

DR. BRENT: Smaller is worse.

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

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

DR. STANKOVIC: Right.

DR. BRENT: Dr. Grieger?

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

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

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

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

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

DR. GRIEGER: Okay.

DR. BRENT: Dr. Duda?

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

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

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

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

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

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

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

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

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

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

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

DR. SCHMIDT: My name is Peter Schmidt. I

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

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

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

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

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

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

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

When we first were made aware of pimavanserin, my first question was, well, do we have data that shows that we really need a new antipsychotic medication? And I went into -- I serve as the PI on a large observational study of Parkinson's patients called the Parkinson's

Outcomes Project. It's been going on for about seven years now. It's got 8,000 patients in the database.

I took this group of patients, and I said, "Let's look at patients who develop psychosis in the third year and how they were doing in the previous two years." And we found that for several years prior to being treated for psychosis, they were experiencing really significant detriments to their quality of life, three times the minimally significant change on average -- a clinically significant change on average on the PDQ-39.

So we feel like there really is a need for better antipsychotic care. And my time is up so I will step down.

DR. BRENT: Thank you.

Will speaker number 2 step up to the podium and introduce yourself? Please state your name and any organization you are representing for the record.

MS. CASAVANT: Good afternoon. Thank you for this opportunity to speak with you today. My

name is Elaine Casavant. I'm a registered nurse, and I work with Parkinson's Disease Foundation on the People with Parkinson's Advisory Council.

I myself am a caregiver and wife of a patient who was diagnosed in 1991 after almost eight years of symptoms that were clearly Parkinson's. He was 46 at the time. We went to the neurologist. He was put on Sinemet and Eldepryl, and had a 10-year plateau of good health, exercise, and enjoyed himself. He was still working. This ended in 2002. Eldepryl was decided not to be effective, and he was placed on one adjunct after another, each problematic, and behavioral issues were terrible.

In 2008, he went through an evaluation, had DBS done in 2009. And again, we had a nice plateau until about 2011. There came a turning point in the disease. He had a cognition, perception, hallucinations, delusions, paranoia, increased insomnia, anxiety, hostility. And these things would vary in severity day to day and would worsen and have continued to worsen over time.

We've used every drug for sleep, anxiety, and all of these symptoms, and some of them have been more problematic than the symptom itself, and none of them have worked very well.

I'm a private person, and I'm just going to give you a quick example. My husband, ever the engineer, woke up in the night screaming and hollering about children in his room. Put the lights on, got him quieted down, convinced him there were no children. He went back to sleep, and an hour later, he was screaming again.

I trotted down the hall and tripped over wire he had strung across the door casing to keep the children out. This is typical. It goes on half a dozen times a day. We need something to help with this.

I am an administrator for online groups of caregivers who train and then go out and start caregiver groups and support groups. And surveys that we did showed that this is the single biggest impediment to home care. We can deal with all the symptoms of Parkinson's, but this is the issue that

will put him in a nursing home. And I would like to be able to have a drug that might possibly give him quality of life and a return to some normalcy.

Thank you for your time.

DR. BRENT: Thank you.

Will speaker number 3 step up to the podium and introduce yourself? Please state your name and any organization you are representing for the record.

MS. CONWAY: Good afternoon. My name is Mary Ann Conway. Acadia has paid for my travel and lodging.

PDP has deeply affected my family for generations. In 1985, I moved to Detroit for a job, and my father called me every day. As time went on, his robust voice turned weak and melancholy. There was something wrong, so after a year, I moved back home.

When I hugged my father, he'd lost so much weight, I thought he'd break. Once a wonderful dancer, he couldn't walk. He shuffled. I heard the word "Parkinson's" after his body seemed to

freeze in place and he'd fall over.

My dad helped our country reach great heights as a control panel production manager for Gemini, Mercury, and Apollo, but my heart sank the day I walked into the kitchen and he introduced me to a coworker. I looked to see where he was pointing. It was an empty chair. He died in 1989.

In 2014, my sister Judy was diagnosed with Parkinson's. She remembered his physical changes. I remembered mental changes. I was shocked when she said there was dignity in jumping off the George Washington bridge, and if I love her, I'd let her go. She was that depressed and frightened.

I love Judy. I'm not letting her go, and that's why I'm here today. Judy was an English teacher and social worker with many interests. But these days, only moments pass before Judy sees snakes on her hands, men in the trees, babies upstairs, dogs at the door, barbershop quartets in walls. She ran out of the house after a car, seeing her daughter in the front seat.

It's dangerous and distressing. She can't

spend time with her grandchildren because of this altered state of reality.

I was dismayed to learn after 30 years not much has changed in the treatment of PDP. Klonopin, Seroquel, Clozaril, Zyprexa were administered and did not relieve her hallucinations, just seemed to worsen Parkinson's symptoms and motor abilities.

Stiffness increased, and Judy became zombie-like. She could not walk unaided as she faltered and fell. She could not get up, down, sit on the toilet, dress, feed, or groom herself. She became a totally different person, sobbing, speaking unintelligible phrases, verbally abusing her husband of 50 years.

Because of the horrible side effects, Judy was taken off all antipsychotics. The stress and demands of the disease and unavailability of any effective drug has thrown the family into chaos. I'm especially concerned for the health of her husband.

Judy told her psychiatrist all she wants is

some normalcy back. The doctor conceded they've tried everything and there's nothing left. I watched as Judy and her husband sat hopeless.

With the approval of pimavanserin, there would be hope, a vast improvement in Judy's daily life, allowing Judy to play and talk with her grandchildren again. My daughter had one chance to sit on her grandfather's lap in 1989. I keep that empty chair as a memory of that day.

You have the chance to bring hope to Judy, our family, hope that we give her grandchildren real memories instead of an empty chair. I'm here today to ask that you recommend the approval of pimavanserin for my sister and so many others affected by hallucinations brought on by Parkinson's disease. Thank you very much.

DR. BRENT: Thank you.

Will speaker number 4 step up to the podium and introduce yourself? Please state your name and any organization you're representing for the record.

MR. THOMPSON: Hi. My name is Ted Thompson.

I'm president and CEO of the Parkinson's Action Network. Because Dr. David Kreitzman couldn't be here today, I'm standing in for him while you watch the video that he provided.

(Videoplayed and transcribed.)

DR. KREITZMAN: Hi. I'm Dr. David Kreitzman, a board certified neurologist, movement disorder specialist, who is submitting this video in regards to your application and acceptance of Nuplazid for approval for Parkinson's disease psychosis.

As you know, this is a tremendous unmet need for patients with Parkinson's disease, and we have no current available tools to treat directly these symptoms associated with the disorder.

I'm a primary investigator who worked for Acadia in the relevant program for pimavanserin, the parent drug, and Nuplazid, and also work as a consult for the company in developing marketing strategies for potential product approval. But I thought my best service to you would be to describe two patients that I enrolled in the trial and the

benefits that they received being on Nuplazid.

The first patient was a patient who experienced visual hallucinations. Here's a patient that often was falling going to the bathroom or urinating in his bed. That was what the presenting symptoms were.

When asked why he was falling while going to the bathroom, he said he was trying to tiptoe around the dogs that were very vicious and would wake up and bark. So when I tried to explain to the spouse that the dogs should probably be moved from the bedroom, it was then that it was discovered that there were no dogs in the bedroom. They were visual hallucinations.

She was also very concerned because he was urinating in the bed quite often, and it became very cumbersome to her and overwhelming that she had to constantly change the sheets and/or take him to the emergency room every time he fell and would fall and bruise himself in the doorway of the bathroom.

Since being on the medication, actually in

the open-label portion of the trial, those dogs basically went away, and he stopped falling going to the bathroom and has stopped urinating in the bed. This is obviously an improvement for him, both reducing his risk of injury and falls, and also greatly improved their relationship because there was less work for her to do -- one less thing for her to do when managing his symptoms of Parkinson's disease.

The second such patient was a patient who had delusions of spousal infidelity who thought her spouse was cheating on her by playing music upstairs in the bedroom on the second floor, literally playing music, although the patient does not play an instrument -- the spouse actually does not play an instrument; or she often heard them having conversations in closets. She would often run up and down stairs, putting herself at risk for falling, and would often run into closets thinking she was going to catch him speaking in the closet.

Since being in the program, these delusions actually reduced significantly, where they were not

bothering her [indiscernible]. From her side of the story, it would happen once in a while, but she knew they were not real. So for her and for he, this was a great improvement in their dynamic as a family and reduced her risk by running up and down stairs.

I hope these were helpful examples. These are what we see every day in clinical practice when we identify patients with Parkinson's disease psychosis and why the necessity of a tool such as Nuplazid would be very effective and helpful for us. Thank you for your consideration.

DR. BRENT: Thank you.

Will speaker number 5 step up to the podium and introduce yourself? Please state your name and any organization you're representing for the record.

MS. PEREZ: My name is Brittmarie Janson Perez. My accent is Swedish and Spanish. A retired anthropologist, I'm the widow of Frank Perez who was afflicted by Parkinson's disease psychosis in the last year of his life and did not

get pimavanserin.

I'm here today because when his doctors could find no medication to allay his terrifying hallucinations, having read about pimavanserin, I contacted Acadia directly and kept in touch. Acadia paid for my travel and lodging, but I have no financial relationship with the company.

My testimony is based on the daily log I kept of my husband's condition. Frank was a calm, strong and supportive man, the kind of person who brings out the best in you. We had been happily married for 40 years when Parkinson's psychosis changed him.

Parkinson's psychosis can be diabolic. The devilishly detailed hallucinations, which haunted Frank stimulated maximum paranoia, preyed not only on his known fears of heights and snakes but also provoking feelings of vulnerability, abandonment and betrayal that he had never manifested before, that he was besieged by gangsters, that he was lost and could not find his way home, that I was having an affair and divorcing him with the approval of

our daughters, and that I had died.

When Frank needed round-the-clock care, I was able to keep him at home by hiring three excellent caregivers at a cost of $4,000 monthly. But finally, we could not control him. A man who should have died in his home surrounded by his loved ones spent the last three weeks of his life in the dementia ward of a nursing home. He died alone at 1:00 o'clock in the morning on the 1st of December 2014.

Financially, the cost of Parkinson's disease psychosis is high. For the victims, the psychological suffering is excruciating. Their families' emotional trauma does not end with their loved one's life. Our memories are scarred forever.

For the sake of the thousands afflicted by Parkinson's disease psychosis whose agony may be averted or diminished by pimavanserin, I urge you to recommend its approval. Thank you.

DR. BRENT: Thank you.

Will speaker number 6 please step up to the

podium and introduce yourself? Please state your name and any organization you're representing for the record.

DR. EBERLING: Good afternoon. My name is Jamie Eberling. I'm a scientist from the Michael J. Fox Foundation. I have no financial relationship with Acadia, nor do I stand to gain financially should pimavanserin be approved by the FDA, although Acadia did pay for my travel today.

People think Parkinson's disease and see a tremor or some shuffling with slow movements and impaired gait. Those motor symptoms are the cardinal features of Parkinson's, but they are far from all that the 1 million Americans with this disease experience. We have gotten pretty good at treating these motor symptoms. However, there are a number of non-motor symptoms that go largely untreated.

Estimates vary, but meta-analyses have shown that more than 50 percent of people with Parkinson's disease may experience what we call Parkinson's disease psychosis. Patients may

experience hallucinations, delusions, illusions, or false sense of presence. Parkinson's disease psychosis and its effects are debilitating, costly, both emotionally and financially.

Unfortunately, we are not able to treat Parkinson's disease psychosis well. First, clinicians rule out conditions other than Parkinson's disease that may be causing temporary psychosis such as infection or dehydration. It is also possible that the medication used to treat some Parkinson's symptoms such as dopamine agonist for tremor and rigidity are causing psychosis. Lowering the dose of the agonist may help, but this may exacerbate the motor symptoms.

The doctor may prescribe antipsychotics to prevent the hallucinations or delusions, but there lies another trade-off. Available antipsychotics block dopamine receptors, and thereby the effect of medication for motor symptoms. Currently treating Parkinson's disease psychosis requires a choice, an ultimatum, either motor or mind.

A new option arises with pimavanserin.

Trials have shown that blocking only serotonin receptors can ease psychosis without interfering with dopamine therapies and worsening motor symptoms. The benefit this could bring to the individual would be significant. Psychosis is disruptive to one's day, to one's identity, and to one's sense of safety. The Parkinson's community, patients and loved ones as well would benefit.

I've been involved in Parkinson's research for over 20 years. At the Fox Foundation, I help to review over a thousand research proposals per year for projects aimed at developing new therapies for Parkinson's disease. We have a broad view of the therapeutic landscape, and in my opinion, Parkinson's disease psychosis is a major unmet need with few largely ineffective treatment options.

The impact of a treatment for Parkinson's disease psychosis would be profound both for patients and their loved ones and would improve the lives of many living with this disease today and the more who will come until we find a cure for Parkinson's. Thank you for your attention.

DR. BRENT: Thank you.

Will speaker number 7 please step up to the podium and introduce yourself? Please state your name and organization you're representing for the record.

DR. FOX-RAWLINGS: Thank you for the opportunity to speak today. My name is Dr. Stephanie Fox-Rawlings. I was previously a neuroscientist at the Children's National Medical Center, and I'm now a senior fellow at the National Center for Health Research.

Our research center analyzes scientific and medical data to provide objective health information to patients, providers, and policymakers. We do not accept funding from the drug or medical device industry. I have no conflicts of interest.

We strongly support the efforts to find safe and effective treatments for patients with Parkinson's disease so that patients can live as independently as possible. Reducing psychotic symptoms is very important, but not when the risk

of harm outweighs the potential benefit. We understand that psychotic symptoms are upsetting and debilitating. The question is, if a drug needs to be taken for the rest of one's life and the drug can shorten one's life, then how much benefit is required for FDA approval?

The data presented today show that pimavanserin provides a statistical improvement in symptoms. However, the average improvement of 3 points or 23 percent on the SAPS-PD scale does not appear to be clinically meaningful.

It is also concerning that the SAPS-PD scale may not test the appropriate types of hallucinations and delusions. Since the scale was the shortened version of the scale for schizophrenia, it focuses on the types of hallucinations and delusions that are prevalent with schizophrenia, but these are not the most common with PDP.

The scale may give undue weight to less common hallucinations like auditory hallucinations, and it does not include related symptoms such as

illusions.

If the drug produces modest benefits with few side effects, it still can be very useful to patients. However, during the 6-week trials, approximately 10 percent of patients taking the drug had a severe adverse event, about twice that of patients taking placebo. This included three patients who died taking the 34-milligram dose as opposed to one taking placebo.

Other adverse events included psychiatric and nervous system disorders, suicidal thoughts, and confusion. Furthermore, patients are expected to be treated for years. Without longer placebo-controlled studies, we cannot predict whether the treatment will provide long-term benefit or if long-term exposure will affect the rate of serious adverse events.

The pivotal study cannot address these questions. The sponsors did provide data for a long-term, open-label study, but we cannot determine its relevance without a comparison group.

Another issue is that the drug does not

statistically improve psychotic symptoms for non-whites, females, or patients under the age of 65 or over 75 years old. However, small numbers for these groups can make this data difficult to interpret.

The drug may be beneficial for a subpopulation of patients with PDP, perhaps with specific types of psychosis or within an age range. However, the current data does not provide enough information to determine if the benefits greatly outweigh the risks for any subgroup.

In conclusion, because of the concerns over limited efficacy, the tests used, and the high incidence of adverse events, we cannot urge you to support the approval of pimavanserin. Thank you for your time and consideration of our views.

DR. BRENT: Thank you.

Will speaker number 8 please step up to the podium and introduce yourself? Please state your name and any organization you're representing for the record.

MR. THOMPSON: Good afternoon. My name is

Ted Thompson, president and CEO of the Parkinson's Action Network. In terms of our financial interest, Acadia did provide local ground transportation for me today, and we have received grants for them for our annual Udall awards dinner and our annual PAN forum. But no benefit would come to us whether this drug is approved or not.

Parkinson's Action Network is a unified voice of the Parkinson's community working on public policy issues. We support an efficient clinical trial regulatory framework that products patients, maximizes limited resources, and considers the full burden of Parkinson's disease.

We do not endorse specific diagnostic products, drugs or therapies, but we are keenly interested in all reasonable ways to expand the number of tools available in our very limited arsenal against Parkinson's.

I'm pleased to stand before you today to speak briefly about the critical unmet need of Parkinson's disease psychosis. PD is often characterized as a movement disorder, but the

realities of the patient experience demonstrate a prevalence of debilitating non-motor symptoms. Such symptoms are equally, if not more challenging, to quality of life as the motor symptoms are.

PDP is a non-motor symptom without targeted treatment options. Studies suggest that up to 50 percent of people with Parkinson's disease are expected to develop psychosis as their disease progresses. Parkinson's disease psychosis can include hallucinations and delusions that worsen in frequency and intensity over time.

The symptom can contribute to an increased risk of hospitalization and institutionalization and can significantly impair the quality of life for patients and their caregivers. PDP can become taxing to the extent where patients require long-term care, and for the greater duration, an average of nearly 100 days longer than those who do not exhibit psychosis symptoms.

Currently, management of PDP is quite limited. In an effort to control the symptoms of the disease, doctors may first consider reducing

medications used to control the motor symptoms and/or prescribe antipsychotics, which can interfere with motor control. These antipsychotics have not been approved, nor have they been proven effective in treating Parkinson's disease psychosis.

Either approach is less than optimal because of the negative impact on motor symptom control and quality of life for the patient. As a result, there's a significant gap in treatment for PDP and what is needed to manage the symptom without potentially worsening the other aspects of the disease.

The PD community applauds the FDA's commitment to development and approval of drugs that address serious unmet needs. We believe Parkinson's disease psychosis falls into that category, and again, not only does that therapy hold great promise for the patient, it can dramatically improve the lives of the caregivers and all those around the patient who is suffering from Parkinson's disease psychosis.

Thank you very much.

DR. BRENT: Thank you.

Will speaker number 9 step up to the podium and introduce yourself? Please state your name and any organization you're representing for the record.

MR. THOMPSON: Sorry. I should have just stayed up here. Again, I'm Ted Thompson, president and CEO of the Parkinson's Action Network. Because Francis Philibert could not be here, I'm standing in for him as you view the video.

(Video played and transcribed.)

MR. PHILIBERT: My name is Francis Philibert from Prospect, Connecticut, and this is my wife Jackie. She's been diagnosed with Parkinson's for over 33 years. And we started this clinical trial in 2004, and we've been on it for 11 years.

To get on the clinical trials, we were approved by Dr. Murphy who had listened to some of the comments that I made, what she was doing such as accusing myself of having affairs, believing it, and so forth.

Also, her hallucination that she was having outside one day, where she was outside and there was a tree we have next to the house. She started yelling, and I had to run out there because I thought she had gotten hurt. But no, it was a boy that was in the tree, and in this tree, it was all covered with bees. Of course, there were no bees there or anything like that. So I just played along, and then she was okay. And she came in.

These are the things that I brought up to Dr. Murphy. And Dr. Murphy thought that we were probably just right for this trial. So we got into the trial. And during the trial, I did find some improvements because she was also accusing me of having an affair. And I found after a while that she was no longer mentioning it. And as time went on, I noticed she was kind of mellow. There was hardly any anxiety. So right now, she's still currently on the two pills.

About a month and a half ago, I found what this trial is all about because before then, didn't know; and found out everything that I had just said

to you about hallucinations, delusions, all of those things had been kind of diminished.

Yes, there were times in the beginning, it was very tough, but this is what I feel after having this clinical trial, that I believe it does work. And I believe that if it does work on what it says it does, which I feel that it did with my wife, that it would help an awful lot of caretakers besides the patient.

So I ask again to approve this, to grant the [indiscernible] so that people's lives, they can have a better quality of life. This is what I find that I have here, a better quality of life. I actually beg you because I really believe in this product. I thank you for listening to me.

DR. BRENT: Thank you.

Will speaker number 10 please step up to the podium and introduce yourself? Please state your name and any organization you're representing for the record.

DR. HERMANOWICZ: My name is Neal Hermanowicz. I'm a movement disorders neurologist

at the University of California Irvine where I treat people with Parkinson's disease. And I have served as an investigator for trials in pimavanserin, and I have also served as a consultant to Acadia.

I am the person in my clinic who makes the diagnosis of Parkinson's disease-related psychosis, and I initiate treatment plans for my patients. I've included some case examples from my practice because I think they're not outliers, but I thought they would be illustrative.

For example, one of my patients who's in his early 70s awakened his wife recently at about 1:00 in the morning. He was in the garage and had deliberately set off the car alarm to summon help, feeling that he was being pursued by intruders who were in his home intending to do him harm. The following day, he asked his wife, "Are you trying to kill me?"

After discussion with his general neurologist within the Kaiser Permanente system, he was initiated on quetiapine. And clozapine

apparently within that system is restricted to some psychiatrists. And in my last follow-up with him, I'm not yet confident that his psychosis symptoms are yet controlled.

Another woman in my practice, 80 years old, has been my patient for 10 years or more, has had auditory hallucinations, which have been very troubling. She hears her deceased son calling her name asking for help. She's also been hearing conversations she believes that her husband is having with a girlfriend that he has hidden elsewhere in their home.

Her husband spends his days bathing her and dressing her and feeding her, and now spends additional time going to the pharmacy once a week for clozapine and also arranging for the blood test for his wife. The drug has been helpful, but it's added significantly to his daily burden.

The last example is another patient of mine in the past who was experiencing hallucinations and some confusion about his wife's identity. I did reduce his Parkinson's medications and discussed

treatment options with the patient and his wife, including quetiapine and clozapine, touching upon efficacy, possible side effects, blood tests that are required for clozapine. And after this discussion, the wife declined the interventions and elected to simply observe the symptoms.

Her husband was later removed from his home by the police, summoned by his wife after he assaulted her in the kitchen of their home under the belief that she was not his wife and was there to do him harm.

The need for additional therapy for Parkinson's disease psychosis is certainly evident to my patients and their family members. It's evident to me in my daily work, and I hope pimavanserin will be available to me to provide to my patients. Thank you for your attention.

DR. BRENT: Thank you.

Will speaker number 11 step up to the podium and introduce yourself? Please state your name and any organization you're representing for the record.

MS. WADE: Good afternoon. My name is Zoey Wade, and I'm from Northport, Long Island, New York. I have no financial relationship with Acadia.

I asked to speak about my grandmother's experience with Parkinson's disease psychosis because it affected our entire family, me in particular. My grandmother and I have been very close my entire life. We've always spent a lot of time together, from the time I was young, memories of babysitting, sleepovers, baking homemade pumpkin pie, and so much more.

The entire family was upset when my grandma was diagnosed with Parkinson's disease. We worried about how she would cope with the motor symptoms, but the reality is that my grandma's hallucinations and delusions are much more challenging to deal with than her reduced mobility.

The hallucinations and delusions made her agitated and nervous. I'd see her constantly peering out the window to check whether there were people in the backyard who might be staring into

the house. In the morning, she'd regularly see a group of adults who weren't actually there doing Tai Chi in the backyard. The idea of strangers in her yard and near her home upset her so much that I often would spend the night in her home to reassure her that she was safe.

It was very upsetting to realize that some of my grandmother's delusions were directly associated with me. She worried and believed that I was in danger when I wasn't at her house, or sometimes she thought she would see me in the room even when I wasn't there, and then get upset when I wouldn't respond to her when she spoke to me. It really hurt me that I couldn't help her understand what was real and what was not.

When my grandmother enrolled in the clinical trial for Nuplazid, we didn't know what to expect or even if she was on the drug, but we soon realized that she must be taking the drug because she really returned to herself. Her hallucinations reduced, and she better understood what was real and what was imaginary.

I was so happy that she seemed like her old self. Her memory and humor are incredible, and I am so grateful to be able to talk with her and spend quality time with her again. She's able to live in her own home and keep her dignity intact. This drug has given my grandma both quantity and quality of life.

I hope the panel today will recommend Nuplazid for approval. It's made such a difference in my grandmother. My grandma needs this medication. I know other families, patients would benefit from having this treatment to try. Thank you.

DR. BRENT: Thank you.

Will speaker number 12 step up to the podium and introduce yourself? Please state your name and any organization you're representing for the record.

MS. WADE: My name is Jody Wade. I'm from Northport, Long Island, New York. I have no financial relationship with Acadia and will not gain financially should pimavanserin be approved.

I'm the youngest daughter of Ruth Ketcham, who asked me to speak on her behalf. My mom was diagnosed with Parkinson's disease and later Parkinson's disease psychosis about eight years ago. My mother is not demented, but she experienced hallucinations and delusions multiple times every single night.

In the beginning, the hallucinations were not necessarily frightening or distressful, but they did become so. My mother believed that people were in her house and watching her throughout the night. It impacted her life, that she no longer would wear nightgowns to sleep in and switched to pajamas so that she would be covered and the people wouldn't see her when she got out of bed.

Coat racks became frightening because she thought that's where the people were hiding. She believed that there were animals in her house at night and we needed to call an exterminator. One night she became so fearful, she believed somebody was outside her back window when she was sleeping. She called 911. She was very frightened and call

us in the middle of the night to say that somebody was outside her home. She was just terrified.

This affected me greatly in that I'm a nurse and I just couldn't help her. It was heartbreaking. I could fix so many of the problems, the motor problems of Parkinson's, but I could not stop the hallucinations or convince her otherwise. There is no one in the world I would want to help more than my mom, and I was afraid that this was going to be the remainder of her life.

My mom started the drug trial because she realized she could potentially help others. It didn't take long before I knew that she was receiving the real medication. I was sure because the hallucinations had stopped completely.

If my mom had not enrolled in this trial, she would have not been able to remain in her own home. We would have had no choice but to place her in a nursing home, which we absolutely do not want to do.

The medication enabled her to sleep through

the night, feel safe and secure in her house, and return to her previous state. She was now well rested. She enjoyed going out and was able to do the things she had done before. Since her motor skills were somewhat intact, without the debilitating hallucinations, she was given years of her freedom back.

Fast forward to today, my mom still lives in her own home, recently celebrated her 92nd birthday, and remains an avid Met fan and can give accurate recaps of every game. So that's our story, and that's why I'm asking you to grant the FDA approval for this medication that's been so very helpful for my mother. Thank you.

DR. BRENT: Thank you.

Will speaker number 13 please step up to the podium and introduce yourself? Please state your name and any organization you're representing for the record.

MR. TYNE: Good afternoon. My name is Brendan Tyne. Thank you for the opportunity to speak before you today. My travel and lodging have

been provided by Acadia. However, I have no further financial relationship with the company, nor do I stand to profit from the approval of pimavanserin.

It is with great sadness that I stand before you today. I am not an emotional person, but I cry at least once a day over what this disease has done to my mom and to our family. My mom was diagnosed with Parkinson's in 2014. When my father called and told me, I was unable to breathe or speak.

This is impossible, I thought to myself. My mom was a rock, always in great health, looked 10 years younger than her actual age would suggest; the kindest, more caring mother a child could ever ask for. This can't happen to her.

I finally choked out the words "I will call you back," and then I hung up. After I collected myself, I called him back, and we began the discussion around what this meant for my mom and how long before she starts showing real signs of this horrific disease. My father was having health issues of his own at the time, and still is, so the

thought of him serving as the primary caretaker for his wife of 50 years was a daunting task, to say the very least.

Early on, the focus was on the physical aspect, although my mom had already shown signs of the mental effects. Over the next year, she declined slightly, but not rapidly. It wasn't until the past few months that things have gone downhill dramatically. My mom cannot move without assistance and has hallucinations almost constantly throughout the day.

She thinks there are people in the house and animals are coming to get here. One night while I was there to help out, my dad woke me up in the middle of the night because my mom had fallen out of bed and could not get up without our help. My dad has to take care of her every minute of every day. She yells at him when he tries to help and cries herself to sleep every night because she thinks he's trying to harm her.

My parents have been happily married for 50 years. They are the epitome of a loving couple

and a true example of what it means to be married. Their 51st anniversary is next month, and I can only assume my mom won't even know what it means.

My dad is so distraught that on Christmas, he broke down in my arms, sobbing about how much he loves her and can't stand to see her go through this. He is also not an emotional person, so to see him like this shows just how much it is tearing him apart.

On top of taking care of my mom, my dad now has to sell the house that they have lived in for 43 years, raised our family in -- and it's the only place my mom has ever considered home -- because it is now unlivable for her. He then has to find a new place to live, all this while he considers the financial implications, healthcare options, deals with insurance, takes her to the doctor, and gets the appropriate people in to help her.

Given that these are all things my mom has taken care of throughout their marriage, it is impossible to overstate how much stress this is adding to my dad's already unconscionable

circumstances.

I have two young children that love their grandmother. If nothing is done to bring her back to some semblance of normalcy, my children will never remember their grandmother for who she really is, a loving, funny, caring woman who has improved the lives of all of the loved ones who surround her.

Please, I beg you, do not deprive my children and their grandmother of experiencing that love. Please recommend approval of pimavanserin for my mom and so many others who suffer with Parkinson's disease hallucinations. Thank you.

DR. BRENT: Thank you.

Will speaker number 14 please step up to the podium and introduce yourself? Please state your name and any organization you're representing for the record.

DR. KREMENS: May it please the committee, my name is Daniel Kremens, and I'm an associate professor of neurology and the co-director of the Parkinson's disease and movement disorder center

and Sidney Kimmel Medical College at Thomas Jefferson University. I currently personally care for hundreds of patients with Parkinson's disease.

Although I have been a paid consultant to Acadia in the past, I have no equity interest in the company, and I am appearing today before this committee on my own time to express my deeply felt concerns regarding Parkinson's disease psychosis, one of the greatest unmet needs for Parkinson's patients.

Parkinson's disease psychosis is one of the dirty secrets of Parkinson's disease. It is not discussed by patients who are concerned that their spouse, children, or doctor will think that they are crazy if they say they are seeing or hearing things. And as insight is lost to the hallucinations or delusions, as happens most of the time in this condition, it becomes devastating to the patients and their families, often leading to nursing home placement and increased mortality.

Mr. Smith is a typical patient, and his story highlights the impact that Parkinson's

disease psychosis can have on patients and their families. He was an otherwise healthy 80-year-old gentleman when I initially diagnosed him with Parkinson's disease and started him on carbidopa/levodopa.

After a year or so, he complained of worsening motoric issues, so his medication was increased. At his next visit, his 83-year-old wife raised the issue that Mr. Smith was accusing her of having intercourse with an 85-year-old neighbor multiple times during the day while Mr. Smith was at work. Mr. Smith admitted that he was angry with his wife and could not believe that she would do this to him after 50 years of marriage.

No amount of counseling could shake Mr. Smith's delusions, and Mr. Smith was not demented. He was still a very successful businessman. Over the next year, I tried every intervention, including ruling out infections, reviewing his non-Parkinson's disease medications, reducing his dopaminergic medicines, which he didn't tolerate; adding quetiapine, which made him

too tired and confused; suggested clozapine, which he refused due to the necessary blood work. Indeed, the suggestion of blood work only increased his paranoia regarding his wife. I tried risperidone, which caused marked motoric worsening and sedation. Nothing helped, and to make matters worse, Mrs. Smith was diagnosed with an aggressive form of cancer.

She was shortly on home hospice, and while she was dying, Mr. Smith routinely accused her of continuing to engage in sexual relations with a neighbor. This caused tremendous pain to Mr. and Mrs. Smith, as well as their daughter who is now bringing Mr. Smith to his visits.

Soon thereafter, Mrs. Smith died, and no one was at peace; not Mrs. Smith, who while dying was berated by the accusations of her husband; nor Mr. Smith, who to this day does not understand the betrayal he believes he suffered by his spouse's alleged infidelity; nor his daughter, who often weeps at her father's appointments while he rages against his dead wife.

Before becoming a physician, I practiced law at a large New York law firm for nearly seven years. I changed my career because I wanted to help people and have a direct, meaningful impact on their lives. Taking care of Parkinson's patients has been remarkably satisfying, and we have made tremendous strides in the motor symptoms of Parkinson's disease.

But despite these wonderful advancements, I still have no safe and effective medication approved for Parkinson's disease psychosis. Current off-label options are either poorly tolerated, lack efficacy, or have serious safety concerns.

Pimavanserin has demonstrated to be generally safe, tolerable, with clinical meaningful efficacy. We must recognize the desperately unmet needs and offer hope to our patients and caregivers who are suffering now. I urge this committee to approve pimavanserin for Parkinson's disease psychosis. Thank you.

DR. BRENT: Thank you.

Will speaker number 15 step up to the podium and introduce yourself? Please state your name and any organization you're representing for the record.

MR. THOMPSON: Hi. Ted Thompson, president and CEO of the Parkinson's Action Network. Because Drew Bourrut was unable to be here, I am standing in for him while you view the video that he submitted.

(Video played and transcribed.)

MR. BOURRUT: I'm Drew Bourrut and live in Smithtown, Long Island, New York. I have no financial relationship with Acadia and will not gain financially should pimavanserin be approved by the FDA.

My wife several years ago had many episodes of hallucinations, hallucinations, delirium, illusions. It was dangerous. She woke up one night, middle of the night. She was in a dream but couldn't tell that she now had woken up; thought she was going to be killed; raced down our hall. And people with Parkinson's can't race, but she

did.

I caught her at the front door. She said, "Am I dead yet?" Collapsed on the floor. It took a couple of hours of talking her down before we could go back to bed. And after that, for months I didn't sleep right because I never knew whether tonight would be a night when she would have one of these episodes.

She also became afraid of her house. When we would go out, when we came home, she would look in our front windows and see it filled with people. Of course, they weren't there, but she became more and more uncomfortable.

So when Dr. Kreitzman told us about the possibility of this experimental drug, we went into the double-blind study. And it became very clear very quickly that Laura was on the actual drug because within a month, the hallucinations, the delirium, the illusions were gone.

She still gets them occasionally. But now she knows that they're hallucinations or illusions, primarily illusions, and she's no longer afraid of

them because she was just terrified of them.

So I really hope that the FDA approves this drug because there are a lot of people out there that have to be on -- who can use this. And it has been just wonderful for my wife.

DR. BRENT: Thank you. I'd like to thank all the speakers for their remarks.

The open public hearing portion of this meeting is now concluded, and we will no longer take comments from the audience. The committee will now turn its attention to address the task at hand, the careful consideration of the data before the committee as well as the public comments.

Dr. Stankovic wanted to address some questions that had been raised that he can now respond to.

DR. STANKOVIC: There were a few questions that stayed open, and we have a few answers to that. There was a question about sponsor's calculation on the NNT and NNH, and there were some different interpretation of those numbers and questions about meaning and how to interpret that.

We have with us Dr. Les Citrome, who is a recognized expert in the NNT and NNH calculations, and I wanted to ask him to provide a few clarifications on the ways how we calculated and how we think about that.

DR. CITROME: Thanks very much. Good afternoon. My name is Les Citrome. I'm a clinical professor of psychiatry and behavioral sciences at New York Medical College in Valhalla, New York. I'm being compensated by Acadia as a consultant.

I'm a big fan of number needed to treat, number needed to harm, and made it a focus of my career for the past 10 years, and I've written extensively on this topic.

NNT and NNH are tools that clinicians use to try and appraise clinical trial results and are used to assist in explaining these to patients. And I just wanted to clarify some of the points being made earlier today about the calculation of number needed to harm in particular.

It's something that I ordinarily calculate for commonly encountered harms when used to assess

the day-to-day decisions that we have when using one drug or another. For example, for antipsychotics, thinking about the rate of sedation, akathisia, weight gain of at least 7 percent from baseline, et cetera. And then to sort of look at these because they are precise. They are commonly encountered enough so that the 95 percent confidence interval is relatively realistic and interpretable.

So for example, recently approved drug for the adjunctive use for major depressive disorder has a number needed to treat for response of 12 -- not all that great, but with a difficult disease like major depressive disorder that has not responded to SSRIs or SSNIs, we'll go for that -- and the number needed to harm for akathisia of 16.

If we take that ratio, we call that the likelihood to help or harm, 16 divided by 12, close to 1. So I do warn my patients about expecting possibly to encounter akathisia, but chances are they'll achieve a response more commonly.

So there's a relatively high degree of certainty with those estimates. Unusual, uncommon harm such as death are difficult to quantify from randomized clinical trials because the numbers are very small. Thus, the 95 confidence interval is usually very, very imprecise. It contains infinity, which means it's not statistically significant, and we can say that it would take an infinite number of patients to be randomized to the test drug versus placebo before expecting to encounter one additional outcome of death. Of course, that's an extreme example, but that's what the data can tell us.

When we try to take the ratio of number needed to harm to number needed to treat, the likelihood to help or harm, with such an imprecise estimate of number needed to harm, it is possible that you are infinitely times more likely to encounter the benefit rather than the harm, which of course, is nonsense.

So what we need to do is exercise extreme caution when calculating ratios of likelihood to

help or harm, NNH over NNT, be extremely careful when using any data that is so imprecise that it's not statistically significant.

So I wanted to make that point, and to address the clinical issues, I want to ask Drs. Isaacson and Ballard to come up.

DR. BALLARD: Thank you. I just wanted to apologize that we didn't fully address the question about what the severity scores meant on the scale. As was highlighted earlier, there were nine items on the SAPS-PD with a total possible score of 45. In my experience, I've never seen a person with nine different psychotic symptoms. Those are a range of potential hallucinations and delusions that a person might experience.

Usually if a somebody has severe psychotic symptoms, they might have one or two hallucinations and perhaps an accompanying delusion. The normal way that we would perceive that to be severe is on the basis of the severity of the individual symptoms, which is quantified on the naught to 5 scale. So with that particular scale, if a score

of 5, an individual symptom means that that symptom is present daily and very impactful. So one or two symptoms at that level of severity would be severe psychotic symptoms in clinical practice.

Just two very brief other things. We heard mention of the clozapine studies for Parkinson's psychosis, and Dr. Andreason mentioned the open-label extension of that study. I'd just like to clarify that in 60 patients over 12 weeks, there were actually 6 deaths in that open-label extension. I think that's important to acknowledge.

Finally, Dr. Stone mentioned the ratio of harm for mortality with atypical antipsychotics in Alzheimer's disease from the meta-analysis. I'd just like to clarify that that wasn't the only consideration in terms of the benefit-harm ratio because the meta-analysis of the same studies for psychosis suggests that the effects size measured by Cohen's d is actually less than naught, .2. So actually the drugs aren't effective as well as being harmful.

DR. ISAACSON: I think that the question about whether these patients truly are moderate or severe, I think as we see in the videos and the patients and the stories that we've heard so eloquently, we can see that even these scores on scales are just a surrogate measure really. The impact on patients, their caregivers, their daily lives, their family, is so immense that these patients who testified by video and such and met entry criteria had a mean of 15, but their symptoms were moderate to severe in how they affected them and their caregivers and their lives.

I think the other point to be made simply is that this psychosis is not happening in a vacuum. It's happening in people with Parkinson's and impaired mobility. And every two, three, or four hours, their mobility gets better, then it gets worse, and they can't move. And then they take their medicine, it may work, and they get better, or it may not work so well and they stay immobile.

This happens four or five, six times a day. And it's on these patients where they

have these terrible psychosis symptoms that you just heard so much about.

DR. STANKOVIC: A couple of other questions, a question on the videotapes or the live interviews done by Medavante, our contractor, there were a sample of interviews taped, primarily for the quality inter-rater reliability purposes, and that is how the high inter-rater reliability of .93 was established. As a routine procedure and for privacy reasons, these sample tapes are later on destroyed after the project is completed.

The question on the PD medications and protocol violation, we had 4 patients that modified their PD medication during the trial. Analysis, when these 4 patients are excluded from the trial, there was no effect on the primary outcome or the outcome of the trial.

Questions to the Committee and Discussion

DR. BRENT: Thank you. We'll now proceed with the questions to the committee and panel discussions. I would like to remind public observers that while this meeting is open for

public observation, public attendees may not participate except at the specific request of the panel.

We will be using an electronic voting system for this meeting. Once we begin the vote, the buttons will start flashing and will continue to flash even after you've entered your vote. Please press the button firmly that corresponds to your vote. If you are unsure of your vote or you wish to change your vote, you may press the corresponding button until the vote is closed.

After everyone has completed their vote, the vote will be locked in. The vote will then be displayed on the screen. The DFO will read the vote from the screen into the record. Next, we'll go around the room, and each individual who voted will state their name and vote into the record. You can also state the reason why you voted as you did if you want to.

We will continue in the same manner until all questions have been answered or discussed.

I just wanted to clarify one thing for us to

consider, which is that it appears that for the subgroup with dementia, that the risk/benefit ratio was more favorable. And I don't know if we need to discuss that further, but that was just an observation that I think we should keep in mind.

(No response.)

DR. BRENT: You can see that I'm following directions well here.

Has the applicant provided substantial evidence of the effectiveness for pimavanserin for the treatment of psychosis associated with Parkinson's disease? So we're discussing now.

Dr. Gerhard?

DR. GERHARD: It's again a question for the sponsor. We had some discussion about the problem in looking at an average score of a -- and how to interpret the reduction when the severity in a sense can -- as Dr. Ballard just pointed out -- may lie in a single symptom or in one or two symptoms.

So a patient might be very severely impaired with a score of 10 if he has two subscales that are at 5, and that person might be significantly helped

if he has a 5 in a symptom category and that goes down to 3. The same would happen to another category.

That would be very different, I think, than a patient that has five subscales at 3, and he goes down to 1 in four of them.

So is there any way that you have looked at this in the sense of improvement, how much of that average affects specific symptom categories or would lower the kind of maximum points in those 5-point subscales?

If I understand correctly what Dr. Ballard was saying, that's really where the severity lies. Rather than the sort of 5 driven by a 1 on five subscales would be very different than a 5 on one specific subscale. I'm not quite sure whether there's a better way to look at that.

DR. OWEN: So the question that I'm understanding is have we looked at it by how many people got better on a one subscale versus those who got better on multiple subscales.

DR. GERHARD: Whether the average

improvement was kind of focused on specific subscales where there was a meaningful improvement, or whether it was kind of more commonly distributed over five, six, seven subscales, where I think the interpretation of the two different scenarios would be very different.

DR. STANKOVIC: The items on the 9-item scale that changed most was the hallucination global item, visual hallucinations and the global item on delusions. Slide up, please.

So as you can see, these are first, second, and then third from the bottom are changes on those items. I will remind you that in the entry criteria for the trial, the requirements on the SAPD-PD was that minimum one item has a score of 3 and one global item has a score of 3 or more.

DR. GERHARD: Just for clarification, this is not -- this is just the raw treated group baseline and post-treatment without placebo --

DR. STANKOVIC: Yes. This is without placebo.

DR. TEMPLE: Do you have a similar slide

that shows effect size for each of those? That is, difference between drug and placebo. That's what you're really asking.

DR. STANKOVIC: We do not.

DR. BRENT: Dr. Duda?

DR. DUDA: John Duda. Actually, I think what he's really trying to get at is do you have a similar slide looking at, for example, how many of the people responded had a greater than 2, say, improvement on a given item, so greater than two steps on visual hallucinations or anything like that?

The one clinical example you gave did have a 2-point -- and I think going from once a day to once a week is a clinically meaningful response, and that would be an indicator of that.

DR. STANKOVIC: We do have cutoffs from 1 to 10 change on the SAPS-PD scale in the score in the pimavanserin arm and placebo arm. We do not have for the individual items, but we do have for the total score from distribution of patients that had one or two or three or so on reduction.

DR. BRENT: Dr. Sarkar?

DR. SARKAR: This is just a comment to the sponsor. In my reading of the participants in the trial, there were two who were not white, and I feel that that makes the generalizability very limited for those of us who are practicing here.

DR. OWEN: I'm sorry. Can you repeat, there were two who were?

DR. SARKAR: Who were not white by race or ethnicity. Not white.

DR. OWEN: In terms of the generalizability of the general population. So we've looked at this from a different perspective. There is a Kaiser database analysis in 1990s of 588 patients, new incidence patients, to get at this idea of demographics in the PD patients.

What we're seeing, or at least what was demonstrated in that study, was that the demographics of the patients who are treated or diagnosed and treated for Parkinson's may not be exactly the same as the demographics of the overall population.

Slide up, please. So this is from that Kaiser database. Eighty percent in that population are white; 5 percent black.

I'd like to invite Dr. Stankovic to talk about subgroup analyses by demographics.

DR. STANKOVIC: I would just want to say that in the clinical trials, the demographic proportion of patients in regard to different demographic characteristics obviously depends on the geographic area where we do. In our overall program, we had about 10 percent of patients that are non-white. Part of that is because also one of the trials was done in India, so we had patients there.

The overall demographic proportion, we would think that the representativeness of the sample that we have comes close, but it's not really where it should be.

DR. SARKAR: I think it's a little bit disingenuous to show a slide from 1994 and '95 in one healthcare system and say that that's what we're doing with Parkinson's. I understand that

recruiting diverse participants for trials is not easy, but I'm disappointed by that response.

DR. BRENT: Dr. Winterstein?

DR. WINTERSTEIN: I have a question for the FDA, I guess, in thinking through what efficacy and what safety data we have. We're looking at one phase 3 study now, which I understand could be considered under the Breakthrough Therapy Designation Act, but I see concerns on both sides.

With the efficacy portion, we have essentially an untested scale in which we learn now has a massive floor effect because it appears that there would be really no patients who would have a 45 score. So that still to me seems to be some hand-selected scale that we don't know really what it means in the context to other drugs that have been tested in this context. And just comparing effect sizes doesn't really seem to address that.

So we have a scale that there's no test/retest reliability that has been done to summarize what Dr. Schmid had asked about. We don't really know the psychometric properties of

this scale. So that's the efficacy portion.

Then obviously, from the safety portion, we really don't have enough data. Of course, we never have when we're looking at phase 3 studies. But I'm wondering what the thoughts are on requiring a second trial, considering I have never dealt with the breakthrough designation before. So I'm curious whether that would be an option.

DR. TEMPLE: Let me start. The concern about the measurement would still be there even if you had two studies, and that's one of the reasons we're coming to --

DR. WINTERSTEIN: The scale could be changed.

DR. TEMPLE: Well, that's a different question. I mean, this study used a number of scales in addition to the primary endpoint, and one of the things that we're coming to the committee for is advice on whether you think that's a credible measurement.

All I'm saying is that the two-study/one-study question turns mostly on whether one study

can be persuasive. And we've written about this, and we've said, ordinarily, we expect more than one adequate and well-controlled study to support a new claim using appropriate endpoints and all that, but that if the effect size is -- if the effect is statistically very significant, and we give an example of like .001, we can choose to rely on a single study. So we can.

But you're raising questions about what the scale means, and I'm not the person to answer that. I think Mitch or others need to address that, but replicating it won't make the scale better.

Now, there might be another scale someone could use, but I think you need to talk about that. I mean, they do use a global also. They had several scales, and they show similar results. But whether we rely on one study is usually a matter of how persuasive the statistics of the finding is. And when we talked to the company, we told them that a very persuasive single trial could be considered to support effectiveness.

But the question of whether you like the

scale, whether you think it's valid, whether you think it's credible, that's not for me to say. That's why we're here.

DR. WINTERSTEIN: The reason I bring this up is a second trial would provide the opportunity of changing that. I mean, we have a scale that doesn't have any formal psychometric testing. I'm a little bit surprised about relying on a scale like that as the primary efficacy tool.

DR. TEMPLE: Well, it was measuring two aspects of the psychiatric problem, and I think one has to decide whether you think it's a good measurement of that, because measuring hallucinations, that's one of the major problems. If you don't think that's a good scale, it's important to think of what would be a better scale.

DR. CHEN: Yes. This is Wen-Hung Chen. I'm from the clinical outcomes assessment staff.

SAPS H plus D, the whole 20 items instrument has been used in schizophrenia. It was developed for schizophrenia and has been used primarily in the schizophrenia patient population. There are

some little research that supports its psychometric properties.

To support for the psychosis in the Parkinson's disease, we have that one study, one paper that was done in showing that reducing from the 20 items to the 9 items. And that one shows some psychometric properties in terms of some of the reliability, correlation with other instruments.

However, like you said, we don't feel it is ideal, but it is acceptable for this indication because of the breakthrough therapy designation and because of some of -- the 9 items cover some of the important relevance in terms of psychosis for Parkinson's disease. So that's why we feel that it is adequate, not ideal, but it is adequate.

We do feel that further improvement in that instrument would be actually even better for the future. But again, for this submission, we feel that it is sufficient to demonstrate that it does cover some of the important symptoms that we are concerned about.

DR. MATHIS: We should point out, too, that the 20-item scale was also significantly different drug versus placebo in this trial. So while we'll never be sure if the 9-item -- well, someday in the future, we hope to be more sure that the 9 items capture what we're interested in. The fact that the 20-item scale may be one that's been around longer and has had its psychometric properties evaluated made me feel better about that.

DR. BRENT: Thank you. Dr. Narendran?

DR. NARENDRAN: My question is somewhat related, but not exactly perhaps. But one of the things is, I mean, this drug seems to be no worse or no risky than antipsychotics for dementia based on the presentation.

So then the question really is, I mean, is it as effective? I mean, what's clinically meaningful? It's statistically significant, but is the 3 point clinically meaningful? I guess that's where the struggle I've been having is.

So it's hard because there are no literature to compare, and the scales used in schizophrenia

trials, BPRS or PANSS, you can't really normalize and say this is where this stands.

The CGI seems to be a secondary measure. The delta compared to the drug to the placebo is only .6 or .5. Is that norm in schizophrenia trials to see that small of a difference? Because it seems like that could be something that could be used to see how effective this drug could be or how clinically meaningful it could be.

I'd also like to hear from the neurologists on this panel to maybe clarify for the psychiatrists like us what is clinically meaningful, if this small number, 3 points or what.

DR. DUDA: John Duda. As one of the movement disorder neurologists here, I want to start out by saying I think from my perspective, and maybe Stan would agree, that the subdivision of the full SAPS-HD into the SAPS-PD has face validity. I mean, the symptoms that they pulled out don't seem to be just cherry-picked because they had the most likelihood of showing an effect.

Those are the ones that are most commonly

seen in PD. Like I think they pointed out, if we had everything we wanted, we'd have a totally different scale that included some of the symptoms that aren't captured at all in there like illusions and presence hallucinations.

But I don't know, from my perspective, we keep talking about whether or not the clinically meaningful difference of 3 points is valid, but it's 3 points over placebo. I mean, to me as a clinician, it's a 6-point difference, right? It's 6 points from baseline to treatment effect.

Yes, to prove that it's better than placebo, we have to look at the 3-point difference, but to determine whether or not it's clinically meaningful, I think we should focus more on the 6-point difference between baseline and the benefit of the treatment.

In that case, like I said, it would have been really nice to see how many patients had a significant improvement on one of those 9 different items. But presumably with an average of a 6-point benefit, I think probably a fair number of them

probably wouldn't have at least a 2-point difference on one of those items. I could be wrong, but that's my perspective.

DR. BRENT: Dr. Grieger?

DR. GRIEGER: I'm going to speak directly to the question. I mean, I think they've demonstrated efficacy, and I think the big differential with this, compared to what we've got now, is the absence of any evidence of a motoric impairment as a result of adding this medication to patients that were already on Parkinsonian medications.

So that's a big plus for this population. It's a difficult to treat population with a lot of primary effects and a lot of side effects in a complex medication regimen. And it showed it didn't cause any harm. And for a number of patients, it showed marked improvement in some symptoms.

To the extent that this is a very pervasive problem in Parkinsonian patients, any improvement -- I mean, a 3-point improvement to me is big deal. If you go from having a symptom every

day to having a symptom twice a week, that's a huge improvement.

I didn't have a problem with the scale for the same reason that you mentioned, that it was derived from their prior studies of what actually shows up.

It's a lot easier -- I use a lot of clozapine, but I work in a hospital so it's easy to use clozapine in a hospital. It's really hard with patients that can't get out to be able to do the lab tests.

So this really fills a niche that nothing else is approved for that's easy to use. And whether it's caused by the addition of the drug or whether it's just that the patients were getting worse and required the drug, there's a study that just came out this week on hazard ratios of patients that are started -- 7,000 paired groups, 7,000 patients paired in each group, who are Parkinsonian patients started on antipsychotics, those not started on antipsychotics.

Those started on the antipsychotics,

olanzapine, Seroquel, and risperidone had a doubling of their mortality within 180 days of starting on the drug. So that's a problem. It seems that if this drug can do something without doing something bad or not doing it much worse than the placebo, it seems to fill a gap.

DR. BRENT: Dr. Duda?

DR. DUDA: Can I just respond to that real quick? The study by Weintraub, et al. should be clarified that it's a naturalistic study, so you really can't separate out the effect of the drug versus the effect of having psychosis in Parkinson's disease.

DR. GRIEGER: Right, I hope I made that clear, but you're absolutely right. It's a naturalistic study.

DR. BRENT: Dr. Ionescu?

DR. IONESCU: I just have a brief technical question to ask about number needed to treat. The FDA had a number needed to treat summary slide -- I think it's slide 31 -- compared to slide CE-28 from the company.

I was just curious to know, I noticed with the company, there wasn't a greater than or equal to 50 percent reduction in the SAPS-PD analysis. And I just wanted to make sure it would be the same numbers that the FDA presented on their slide. I just wanted to make sure.

DR. STANKOVIC: The numbers that we presented are based on the all-20 clinical trial. FDA, Dr. Andreason presented both that and then exploratory analysis that he did while including the other trials that were not either completed or failed.

DR. IONESCU: Okay. Thanks.

DR. BRENT: If there aren't any further comments -- oh.

DR. SCHMID: I was just wondering if there was any data on long-term efficacy beyond 6 weeks.

DR. STANKOVIC: Yes. In addition what we presented, we do have data for all of the patients that converted from the double-blind trial into open-label trial. We still kept following enrollment in the open-label trial. We still kept

separation of their prior randomization in the trial, and here is the data. I would like to point out that, obviously, we are looking at long-term uncontrolled data.

Slide up. As you can see, similarly what we present up to 10 weeks, the people in gray that were on placebo, within the first 4 weeks of the open-label trial, came to similar efficacy as the patients that were in the pimavanserin arm in the double-blind trial. And then pretty much up to 30 weeks, they maintained that.

These are the patients in study 020 that converted into the trial. We have another graphic -- slide up, please -- presenting all patients from all trials that are in the open-label trial, and this is their efficacy data.

Once again, as we go further into here, we have a pretty good retention because up to week 30, we lost about -- we have retained 75 percent of the patients up to week 30. But as we go further, we have data obviously for longer, but the dropout rates continued to creep up. Although, like I

said, for this type of trial in psychosis, up to 30 weeks, retention of 75 percent is quite impressive, actually.

DR. SCHMID: So let me just summarize that. So it looks like for the CGI outcome at 30 weeks, there was no difference between the two groups. And do you have the primary outcome? Do you have any information on primary outcome?

DR. STANKOVIC: Primary outcome was only measured after first 4 weeks. Later on, it was only a CGI, the Clinician Global Impression.

DR. PICKAR: Question to the agency, to you folks, the way it's phrased, is effectiveness for the treatment of psychosis associated with Parkinson's disease. And not to beat the old horse, but really what you're treating is psychosis associated with treatment of Parkinson's disease. There's no untreated person in this study.

As I know broadly, but not being a neurologist, that it's not common to see a psychosis associated without some treatment. And what you're doing is you're giving dopaminergic

agents, which are known at every level, according to the FDA, that one of their side effects is hallucinations and delusions. It's in the package insert for levodopa and probably is for the dopamine agonist.

So my question, is this phrased correctly because that doesn't sound -- it seems to me that you're treating a drug side effect, and I don't know if that's overly picky. I'm willing to hear other people's opinions. But it just is a little bit funny the way it's stated here. And I don't think the data demonstrate that, but they do demonstrate improvement when you get these kind of -- I'm calling them side effects unless neurologists would tell me otherwise.

I don't know how else to interpret these psychotic symptoms treated with -- I don't even know dosages, but presumably pretty aggressive dosages of Sinemet over many, many years.

So I just want to know, is this statement actually correct, assuming that the data says, gosh, it's really doing the deed? Is this

statement even correct?

I'm looking at the neurologists. I always like putting them on the spot. But seriously, what we're treating, is this Parkinson's disease or is this drug-induced adverse events or symptoms? And the drugs involved are known, certified by the FDA, to produce hallucinations and delusions. And it has broad implications to how this drug is going to be used by clinicians. That's why I'm saying it.

People will use it off label in a much more broad way if you leave it in this, affecting the psychosis of an illness versus a drug-induced psychosis. It will be very different use of this compound. And we heard the sponsor speak a great deal about calling it an antipsychotic. Each time I got a little twitch. Never found out the data in real psychotic patients. But you're looking at psychotic symptoms in drug-treated patients by drugs that cause psychosis.

DR. FAHN: So may I address his question?

DR. PICKAR: Yes, I'm asking advice.

DR. FAHN: So you're absolutely right. I

mean, all these people are treated. The drugs themselves are probably contributing, if not the sole cause of the psychosis. Certainly, people with Parkinson's disease, even before they get on medicine, maybe could have some symptoms like with dementia with Lewy body symptoms. They could have hallucinations.

But generally, what we see are people who are treated with Parkinson's disease, who then develop their psychosis on the drugs. So is the disease itself causing the psychosis, if that's what you're asking, or is it the drugs that they're treated with causing the psychosis?

DR. PICKAR: I'm looking at the -- I'm getting very concrete in my -- I'm looking at the label and what this has proven.

DR. FAHN: My interpretation when I read this is that it says, "associated with Parkinson's disease." It didn't say that it's caused by Parkinson's disease.

DR. PICKAR: They do not have one patient there without treatment, not one patient.

DR. FAHN: But even so, it doesn't -- let's say you had a patient who has psychosis with Parkinson's, and there will be some patients -- if this drug does not worsen Parkinson's disease, it might be a very good treatment for it. Did they have any patients like that? Probably not.

DR. PICKAR: The issue is what they've demonstrated. I understand the wish list. I just want to know -- we're asked a very specific question I'm trying to grapple with. Have they substantial evidence for that statement?

DR. FARCHIONE: I think that the issue here, the use of the word "associated" is not by accident. We don't know whether it's the disease causing the symptoms or the treatment of the disease that's causing the symptoms, or both. But the fact is that there is psychosis involved, and it is in this population of patients who have Parkinson's disease. So the two, they hang together, and whatever the causation --

DR. PICKAR: And they're associated with people who are given drugs that cause psychosis.

That's a fact. That's an FDA label. Now, you can't tease it apart. I'm going to be sticky about this. This is going to huge implications in the real world.

DR. FARCHIONE: Right. But I think that the question is not so much what the implications for labeling are going to be because we'll describe the study population and everything like that. The question is just whether or not they have established substantial evidence for the treatment of these psychotic symptoms that happen to be in this population that has Parkinson's disease.

DR. TEMPLE: He knows that. He's just worried about how we're going to describe it.

DR. FARCHIONE: Yes. But I mean, the labeling is going to be a separate question for later. And like I said, we'll always describe the population that was part of the study.

DR. PICKAR: I would have a problem if the label said this, and that's what we're voting on. So I'm very self-centered. How do I vote on this? I would have a problem with this label.

DR. TEMPLE: Is that because you're sure it's the drugs that do it?

DR. PICKAR: I'm sorry?

DR. TEMPLE: Is that because you think it's obvious that it's the drugs that are causing it?

DR. PICKAR: No. I just think that's what you're asking, what does the data show.

DR. TEMPLE: No, I know but --

DR. PICKAR: And that's what it shows.

DR. TEMPLE: -- let's say in the end, we don't have enough data on psychosis in people who aren't treated because how do you get untreated people with bad Parkinson's disease?

DR. PICKAR: Well, for example, there are 200 patients treated with schizophrenia. I didn't hear one piece of data on the same variables that are here. So maybe it's unique to Parkinson's disease. But there's data out there, and that's how it's going to be used, Bob. That's the problem.

DR. FARCHIONE: But we also don't know that the psychosis in the same in Parkinson's disease

and schizophrenia. Even the way that it manifests is different with more visual hallucinations in the folks with Parkinson's disease, more of these delusions about infidelity. That seems to be a recurrent theme versus the aliens are putting stuff in my brain. It's a different kind of thing. And without knowing the pathophysiology of the individual, it's hard to say.

DR. PICKAR: I don't think it's that different.

DR. FARCHIONE: I know it's not. I'm just --

DR. PICKAR: And too, when L-dopa, when these drugs cause a psychosis, visual hallucinations are common. Those are drug effects, and psychosis is just not that common. When you're starting to do dopaminergic influences, you get organic-like psychosis, which is what this is.

DR. TEMPLE: It sounds like you'd like to see it say associated with levodopa-treated Parkinson's disease or something --

DR. PICKAR: Yes. I just want it to

accurately reflect what the trial is.

DR. TEMPLE: Okay. Well, we'll think -- we'll certainly -- we would think about that. That's a good question.

DR. PICKAR: Great.

DR. MATHIS: Psychosis associated with Parkinson's disease or its treatment; is that what you're thinking?

DR. PICKAR: With treated Parkinson's, associated with Parkinson's disease who are treated with dopaminergic agents. Ninety-eight percent were treated with L-dopa.

DR. TEMPLE: We'll think about that. It's a good thought.

DR. BRENT: Ms. Witczak?

MS. WITCZAK: Yes. I was going to reiterate what you said because that's a big concern, because it's one thing if it's -- because that's everything that I've seen and talked with patients, and it is the drug-induced.

So if we are going to be giving another drug on top of a drug, I think we need to have that

question in here because I think the efficacy on what they showed us is really more about the treatment for Parkinson's disease.

Because I can just see the press releases and everything else and the way it will be communicated to the general public if we don't really answer that question upfront and do it the right way.

DR. TEMPLE: Can you say more about that? Are you worried that it would be extended to people who don't have Parkinson's disease? I thought that was the worry that was being expressed.

MS. WITCZAK: Yes, that's one of my concerns is that it will eventually be used as off label, especially as we know the way things are going in Congress.

DR. TEMPLE: Okay. But in that case, it doesn't really matter whether you're treating something that the Parkinson's -- well, maybe you think it does.

You're saying if it's only people who are responding to their treatment, then people wouldn't

believe that it would work in someone who didn't have Parkinson's disease. But if it was treating the underlying disease, which happens to also be treated, then they might. That's fine.

MS. WITCZAK: Yes. I just think we need to be really clear about what we are looking at the evidence for.

DR. PICKAR: And when we vote, it has to be exactly as the question you presented us, correct? I'm just asking.

DR. TEMPLE: Well, we're listening to what you said about that. We appreciate that.

DR. PICKAR: No, I appreciate that. I'm just trying to answer the question to my sense of what the presentation was, what it showed, and what the statement would be. That's all.

DR. BRENT: Dr. Duda?

DR. TEMPLE: So are you wishing that we put with treated Parkinson's --

DR. PICKAR: I can't approve it stated like this. I don't think they've demonstrated that. I think they've demonstrated in what that population

is.

Bob, this is a breakthrough study. You're doing it one study, not two. You're moving this very fast. I love it. I love it. I'm a doc. I want these things out there, but be careful on the clinical designs and so forth, and be accurate.

I was very disappointed I didn't see more data about its treatment in other psychoses. This is a one-shot deal, one study. So if it's a one-shot study, boy, that's got to be good, and there shouldn't be any questions.

DR. TEMPLE: Are we allowed to revise the question? Can we?

(No response.)

DR. TEMPLE: Let's say we're going to interpret that question as meaning "with treated Parkinson's disease." I don't think that's a problem, and we can do that. It refers to "with treated Parkinson's disease."

I also want to correct one other impression. Breakthrough doesn't mean you get by with less data. There's been a couple of comments that

suggest that's true. The standard for approval, the legal standard doesn't change. We do a whole lot of things to be flexible and encourage good design and all kinds of other stuff, but the legal standard for approval is the same.

DR. BRENT: This is David Brent. So my question is, are we rewording the question?

DR. TEMPLE: Yes, I would put "treated" in there.

DR. BRENT: So I think we should have it in black and white so the people know what they're voting on.

MS. BHATT: Right. And if FDA can tell us what you want us to write, we'll make the edits to the question if you want to change the question.

DR. TEMPLE: Well, we're doing this on the fly, but how about if we put "treated" in front of Parkinson's disease?

DR. PICKAR: How would the neurologists feel about that? Would that be okay with you guys? You're a separate club over there?

DR. DUDA: We didn't have a big problem with

it before that, frankly.

MS. BHATT: Is it possible if we could answer this question and then have a 1A question?

DR. DUDA: From a movement disorder neurologist perspective, if you really want to change -- I mean, because I don't know where it ends because you could say Caucasian and you could keep narrowing it down.

DR. TEMPLE: We will understand --

DR. DUDA: If you really wanted to make it more appropriate --

DR. TEMPLE: We will add the word "treated" to it, either in our brains or on there, but that is what you'll be voting on. Okay?

DR. DUDA: This is Parkinson's disease, treatment-responsive Parkinson's disease.

DR. PICKAR: You've got a drug-induced problem here. That's what I'm saying, and it's not recognized as that.

DR. GRIEGER: Are there any? Are there any Parkinson's patients that have hallucinations that aren't under treatment? Does that ever happen

where it's proven that it's from Parkinson's?

DR. DUDA: You can certainly have patients who have Parkinson's disease develop hallucinations from treatment, and then as part of the management of that psychosis --

DR. PICKAR: Not from treatment. How about non-treated?

DR. DUDA: You take them off all of their dopaminergics --

DR. PICKAR: Yes, yes.

DR. DUDA: -- and they can still have hallucinations.

DR. PICKAR: How common is that?

DR. DUDA: In advanced patients, it's not that rare. It's essentially the same as you see in dementia with Lewy bodies.

DR. PICKAR: So associated with dementia of Parkinson's.

DR. DUDA: Yes.

DR. GRIEGER: So you might want to use this agent.

DR. DUDA: You certainly might want to use

this agent.

DR. FAHN: So what dementia with Lewy bodies is and what Parkinson's disease dementia is, just two ways of looking at it, they're probably the same disease. And people with Parkinson's disease notoriously get dementia usually when they're in their upper 70s or into their 80s. Most people will have dementia, and with their dementia, they'll have hallucinations.

If the person wasn't treated, like a person started out with dementia with Lewy bodies, they would have hallucinations. Although this drug wasn't tried on that population, so we can't address it. But this is probably a drug that could be used. It certainly was not going to make their Parkinson's symptoms worse.

So that's what's going to happen in the open market, off label. It will be used for that kind of disease.

DR. PICKAR: What's going to happen off label is it's going to come to our clinic, and we'll be seeing it psychiatrically; so off-label

use in a broad statement, and that's an issue.

DR. DUDA: Except for dementia with Lewy bodies, which still comes to us. Dementia with Lewy body patients would still come to movement disorders and dementia specialists, and it's certainly going to be used for that off label, I would expect.

DR. BRENT: I think we need to call the question, and my understanding is that we have to call the question as written.

MS. BHATT: Yes. If we can answer the question, and then we can just incorporate everybody's comments, and we can put that into the minutes. I think that's going to be a lot easier than reinventing the question.

Is that okay? Is that acceptable to the division?

DR. TEMPLE: Yes, that's fine.

MS. BHATT: Okay. So if the chair could please read the question again.

CAPT ANDREASON: I just thought I can pull up a reference to help Dr. Pickar's question.

This is from an article by Friedman in 2010 on Parkinson's disease psychosis, and the etiology of the hallucinations has been a point of debate for years. Back in 1999, it was thought -- as a matter of fact, when the clozapine article was published, it was published under the heading of Treating Drug-Related Psychosis.

In 2010, I quote from Friedman's article, "The most convincing report of hallucinations occurring in untreated Parkinson's disease patients comes from Tanzania where five of 32 patients had hallucinations, primarily of people or faces mostly seen in their homes. Four of these had never been on medications, and the fifth on benzhexol."

So nowadays, it's really rare to see somebody who is untreated. And within the first year of treatment, the rate of hallucinations doubles, I think, if I'm getting that number correct. But it goes up significantly within the first year of treatment.

DR. BRENT: Dr. Narendran?

DR. NARENDRAN: I do want to comment to,

Dr. Pickar, your question. Well, I have a comment for your thing.

I think etiologically, schizophrenia is definitely a pro-dopaminergic, high dopaminergic disease. But Parkinson's disease hallucinations are also very related to 5-HT2A. There's a couple of PET studies that have shown up regulation of 5-HT2A in the brain in PDP. And if you look at the schizophrenia literature, 5-HT2A typically is negative. There is no real finding in PET. And if you think about LSD as a drug, which also has very hallucinogenic effects and more visually linked, it has what you see in PDP and not necessarily linked to psychosis.

So I think, mechanistically, they're slightly different. I don't think we should tease apart it. I think that wording as it stands is probably okay.

DR. PICKAR: Okay. Thank you.

DR. BRENT: Dr. Ionescu?

DR. IONESCU: Just one question regarding slide CE-9 from the company. That was the

inclusion/exclusion criteria, and this might help with this question, too. I noticed that patients had to have Parkinson's disease for at least a year before coming to the study and then they had to be psychotic for at least a month.

Was there anyone enrolled in the study whose psychosis was longer than their Parkinson's disease?

DR. STANKOVIC: No, because the criterion was that the first Parkinson's disease occurred prior to the psychotic symptoms, and that is really a diagnostic criteria for Parkinson's disease psychosis.

DR. PICKAR: Did you withdraw the people from the antipsychotics before they entered the study, or was that an exclusion criteria? Or did you do that as part of the study? Earlier you said that you stopped their antipsychotic during that period.

Were these people who were on the antipsychotics, or whatever, stopped, waited 3 weeks, and then added this study? You're making

a lot of moving parts in a CNS pharmacology study.

DR. STANKOVIC: There was a minority of patients in the trial, about less than 15 percent I believe overall, that were on antipsychotics going into the trial. But they had to stop that antipsychotic at least 5 half-lives prior to randomization.

I would like also to point out that that doesn't mean that these patients have never been on antipsychotics. They were just not currently, immediately before the trial, on the antipsychotic treatment.

DR. BRENT: Okay. I think we should take a look at the question again. So I'm going to read it again, and I think we should vote.

DR. SCHMID: Can I ask a question? Are we discussing before each question? So we're voting on --

DR. BRENT: Yes, we're just voting on this.

So the question is, has the applicant provided substantial evidence of the effectiveness for pimavanserin for the treatment of psychosis

associated with Parkinson's disease?

Please press the button on your microphone that corresponds to your vote. You have approximately 20 seconds to vote. My 20 seconds starts after I finish talking, right?

Please press the button firmly. After you have made your selection, the light may continue to flash. If you are uncertain of your vote or you wish to change your vote, please press the corresponding button again before the vote is closed.

(Vote taken.)

MS. BHATT: The voting results, yes, 12; no, 2; abstain, zero; no voting, zero.

DR. BRENT: We'll go around the room, and each person should say how they voted and why, starting with Dr. Elmore.

MS. ELMORE: Susan Elmore. So, obviously -- well, first of all, I voted yes. And there are obviously limitations of this study, a number of variables that we've discussed here today. Some could not be controlled based on the

nature of the disease, and these may or may not have had an effect on the outcome and the interpretation of the data, but we really don't know.

My vote was based on the totality of the data, but my disclaimer here is that I would have preferred rather than use the word "substantial," I would have used "some" because that's just the way that I look at the data. To me substantial would have been, just as an example, going from a scale of 4 or 5 to a 1 or a zero. So that's my comment.

DR. TEMPLE: Can I just comment?

DR. BRENT: Yes.

DR. TEMPLE: Substantial refers to the evidence, not the effect size, just in legal terms. It means convincing or whatever you want it to be --

MS. ELMORE: Okay.

DR. TEMPLE: -- not whether the effect is as big as you'd like.

DR. SARKAR: I'm Urmimala Sarkar. I voted yes, and I voted yes because I believe that there

is a benefit that they've demonstrated with a reasonable degree of certainty. And there is a much larger uncertainty about the potential harms.

Therefore, I thought it was more public health forward to approve the drug with the understanding that much more work is needed to ascertain the frequency and severity of the harms that will be associated with it.

DR. GERHARD: Tobias Gerhard. I voted yes. I believe the data, despite some concerns about the scale that was used, is pretty consistent with the secondary outcomes and so on. We all would want the effect size to be larger, but it's certainly convincing in the sense that it is there, and it is meaningful.

DR. WINTERSTEIN: Almut Winterstein. I voted yes for the same reasons that Dr. Gerhard just mentioned.

MS. MORGAN: I'm Linda Morgan, and I voted yes. And the reason is that it seemed effective to me.

DR. SCHMID: Chris Schmid. I voted yes.

I'm not real convinced with the amount of data. However, given the consistency of the outcomes and also the consistency across the two or three studies they've done, which all seem to at least point in the same direction, I was reasonably convinced.

I am still concerned a little bit about the subgroup effects and looking forward to the discussion on that.

DR. GRIEGER: Tom Grieger, I voted yes for the reasons I already stated.

MS. WITCZAK: Kim Witczak, and I voted no for a couple reasons. First of all, because of the discussion we had earlier with putting treatment associated with Parkinson's disease. Also, with the number of people in this clinical trial, it doesn't seem as it's as robust as it should be.

So for those reasons, as well as the type of people that were included, the ethnicity and the background.

DR. PICKAR: I voted no for reasons that are obvious. I would have voted yes had you added that

word, Bob. So I figured this will at least get your attention to how you spell out the label, and you'll think of me when you do it.

(Laughter.)

DR. BRENT: I think I can stop laughing now.

David Brent. I voted yes. I felt there were multiple conversion scales that all showed the same finding. And of course, we'd like more than one positive trial, but this was the only one that was really designed to take in more severe patients.

I was also persuaded by the fact that there really is nothing else, so even if the effects are modest, you have to compare to what is available right now, which, as we've been presented, is nothing.

DR. IONESCU: Dawn Ionescu. I voted yes. I thought the medium effect sizes were pretty good. Especially as a depression researcher, I can completely understand how needed new medications are for these difficult to treat conditions.

The other thing I want to applaud the drug

company for doing is using external raters. I think that's kind of a new thing that's coming online, and I think it's really important. It cuts down on bias. They have nothing to gain from saying that your patients are getting better or worse, and I think that was a really good part of the study design.

DR. NARENDRAN: Raj Narendran. I voted yes. I thought the company did a good job and convincingly demonstrated that it was effective.

DR. FAHN: Stan Fahn. I voted yes. As was pointed out by others also, there is really nothing out there. This drug does not worsen Parkinson's, which is really key factor.

I was disappointed that the efficacy seems less robust than I would have liked. I'm not sure about that. Once we get it in our hands and work with it, we'll see how good it really is. But it's certainly better than nothing. And it does help people, and that's why I voted yes.

I was also disappointed with the fact that it was immediate effect. It took about 4 weeks at

least to get the improvement to some degree of benefit there. But again, maybe newer classes -- not classes, but newer versions of this drug will come out with more power, and is sooner acting, and so forth.

So I think this is a good starting point. I'd like to see it being used for that reason.

DR. DUDA: John Duda, and I voted yes. And I think one of the other things that was compelling to me was that these are patients who had an average of three years of psychosis, suggesting that the typical management strategies, including using clozapine and Seroquel, which are effective in many patients, were probably tried and probably failed in a lot of them, so making it an even more convincing argument that this was effective.

DR. BRENT: I'd just like to summarize the statements. The majority of us voted for the first question. The general tone was that although we would have liked to have seen a bigger trial and a stronger effect, that in the context of this disease and the lack of other readily available

treatments that are easy to use, that this represents a step forward.

There was concern raised about whether the question should have been focused on drug-treated Parkinson's rather than Parkinson's per se. And I think that the general tone of the response of people's discussion was that that is how people come to us, at least in the United States. But there was some discussion about how the labeling should be to reflect the fact that in these studies, almost 100 percent of people were treated with some kind of a dopaminergic agent.

We're now ready for question 2, and I think we'll follow the same procedure. We'll have discussion first.

Has the applicant adequately characterized the safety profile of pimavanserin? So the question isn't whether it's safe or not. The question is whether it's been adequately characterized, right?

MS. BHATT: Yes.

DR. BRENT: Okay.

DR. SCHMID: So here's where I'm going to raise the subgroup question. I think Dr. Brent referred to it earlier. We had the breakdown by the MMSE of 25 greater or less, and I believe the count was 12 to 5 in the higher group, and that would make it 4 to 5, I think, in the lower group.

So to me, that's an important distinction, and that would be very important to me in knowing whether this has been adequately characterized or not.

DR. DUDA: Maybe I misunderstood, but they did characterize the safety issues in both of those groups. You're just taking about the risk/benefit ratio, which is the next question?

DR. SCHMID: Well, I guess what I want to know is whether -- I haven't heard any discussion about the safety being worse in one group than another, and that to me suggests that potentially in the people who are worse off to start with, there's more safety risk than in the other group. So I'd want to know that.

DR. BRENT: Dr. Narendran?

DR. NARENDRAN: My question to the FDA, in the briefing document, the nonclinical toxicology section said that there's some phospholipidosis in the lung. I mean, presumably the way it was worded there was this would be a short-term treatment. Most of these people, they live for an average of two to three years.

But if we're talking about putting younger people, like in their 50s or something, or 40s -- early Parkinson's people are put on this drug and they stay on there for years -- that could have an impact. I don't know. How do you tackle that? I don't know if you could -- that wasn't brought up in the morning, so if you could --

DR. ATRAKCHI: Aisar Atrakchi. I'm a pharmacology supervisor, Division of Psychiatry. The findings for -- it's a CAD drug, cationic amphiphilic drug, and as you probably know, these drugs cause phospholipidosis by their physical and chemical properties. And it did cause phospholipidosis in animals and as early in two weeks in mice, I believe.

So nothing unusual about this. There are a lot of drugs that cause phospholipidosis, and they did cause in this case chronic inflammation. So that's really with longer-term use.

In terms of what would be done with it, it's just you remove the drug. The phospholipidosis presumably will go away. But in some of the studies, there was not complete reversal of the phospholipidosis when they removed the drug. Clinically, I can't answer that for.

MS. ELMORE: And you're speaking of pulmonary phospholipidosis, specifically?

DR. ATRAKCHI: Phospholipidosis was in multiple tissues and organs.

MS. ELMORE: And so the inflammation --

DR. ATRAKCHI: The inflammation was in the lungs.

MS. ELMORE: Okay.

DR. BRENT: Dr. Grieger?

DR. GRIEGER: The simple answer is I think they characterized it appropriately, but it is a small study. And if there's a program of

heightened postmarketing surveillance that could be incorporated to gather that data more consistently for a period of time after the drug reaches greater usage, I think that would be highly beneficial in a subsequent reevaluation of the safety profile and the need for any boxes or warnings.

CAPT ANDREASON: If I could address that question. Thirteen of the 16 serious adverse events were considered not drug related. The adverse event reporting system is voluntary, and people, even if they think it's drug related, often don't send in a report. But they don't send in a report if they don't think it's drug related.

Therefore, I don't see the spontaneous adverse event reporting system as being an adequate postmarketing safety tool.

DR. GRIEGER: I would agree with that having worked in hospitals and knowing what gets turned in and what doesn't get turned in. But I guess what I was suggesting, is there a possibility for something that goes just a bit beyond the normal adverse drug reporting for a period of time,

something more like the clozapine REMS system where you'd have to report something in once a month on negative outcomes.

CAPT ANDREASON: We actually did consider something like this, but we couldn't figure out exactly what to monitor. We don't know that there is a pathophysiologically unifying mechanism, and so we don't know exactly what to tell people to look out for.

The serious adverse events and deaths appeared to be commensurate with what you'd expect in a course of the treatment of Parkinson's disease, but what we see is greater numbers. And this is exactly what we see in the Alzheimer's population.

So again, postmarketing, unless it's a large, simple controlled trial, we don't think is going to show anything that's going to be useful.

DR. TEMPLE: But, Paul, if there were particular concern with some pulmonary fibrosis or something like that, it's not out of the question that a registry of people could be used to identify

such people. It won't get all deaths. That needs a controlled trial, but we can certainly think about that. That's not terribly burdensome.

CAPT ANDREASON: True, there --

DR. TEMPLE: Limiting use to a particular clinic or something like that, that's a very burdensome thing. People were not entirely happy about clozapine, but a registry of a thousand people to see if there's a pulmonary thing, that's not out of the question.

DR. BRENT: Dr. Gerhard?

DR. GERHARD: So I started out with a question, and it became even more to the point, I guess. Initially, I just wanted to ask the question what "adequately characterized" in this context means, whether it means adequately to meet requirements for approval, which I believe is what it would mean because obviously, as was stated earlier, we never know enough about the safety of a drug from clinical trials, certainly not from fairly small clinical trials when compared to other indications here.

Given the question, though, of what should be done to -- even if this is adequate for approval going forward -- better characterize it and better quantify the risks associated with the treatment, which I think is necessary, I would agree that postmarketing observational research is very limited here because we're looking at a very severely -- an elderly population with severe medical problems that occur, whether or not patients are treated, just at somewhat different rates.

To quantify this correctly, certainly with adverse events reporting, is impossible, probably even -- and the details would have to be discussed with observational studies or things like Sentinel. You need some kind of large simple trial. And I think for some of the outcomes like mortality, it should be something that's doable. And I think would think it's something that should be considered as a postmarketing requirement.

I don't know whether the comparator here would be placebo or whether the comparator should

be something like quetiapine in this context. I don't know enough about the specifics. But in order to better quantify the safety issues, and particularly in the context of whether the safety concerns for severe adverse effects potentially are larger than in the second general antipsychotics, I'm not sure that -- we clearly don't know. The confidence intervals are very wide. Everything to me would point that they're similar, but it would be good to know that they're not of greater magnitude.

MS. ELMORE: I'm Susan Elmore. I just want to touch on a couple of points that have been brought up. As a veterinarian toxicologic pathologist, I am concerned about the animal studies. And one thing about the lung is that if we're seeing chronic inflammation in those patients that are treated longer with this drug, that can, as we've seen in the animals, result in fibrosis, which is irreversible once treatment has stopped. So that is of concern, would that also happen in patients treated with the drug.

So I think that this postmarket evaluation is important, and the other significant animal lesion was renal disease. I think that that's why I had that original question, was there specific monitoring of pulmonary and renal disease in any of these patients?

So that didn't happen, but I think that going forward, that would be something to consider.

DR. DUDA: As I recall, it wasn't presented this morning, but I thought there was data regarding the dosing equivalence of the animal studies compared to the human dose.

Can the sponsor comment on that?

DR. OWEN: To answer the dosing equivalence and others, I invited Dr. Wolfgang, please.

DR. WOLFGANG: Grushenka Wolfgang. I'm a toxicology consultant for Acadia. I've been paid for my time to attend the meeting, but I have no financial interest.

So in terms of the question about, essentially, is there a safety margin. For the initiation of the event of the phospholipidosis,

there's a 5-fold safety margin. For the chronic inflammation, it's a similar margin.

I will point out that this was a high-dose lesion. It occurred in the rats at a dose that was above the maximal tolerated dose. And also, in our lifetime -- in the rat carcinogenicity study, where we were just below that maximum tolerated dose, there was no incidence of lung fibrosis, although we did have the phospholipidosis. That was one finding that consistent across the studies.

The other important point about this finding is that it's histologically distinct from what you would expect in a diffuse human lung fibrosis. So that's important. And I think lastly what's important is the dose-limiting toxicities that were seen in the early clinical trials. We probably could not reach an exposure level in humans that we could reach in these animal studies to produce that effect.

DR. OWEN: And for additional comment, Dr. Stankovic.

DR. STANKOVIC: I would like just, if I may,

to add regarding the further studies to assess the risks in this respect. We're already planning, as Dr. Demos mentioned earlier, an observational study on 50 sites in 750 patients to follow up for a period of three years. It would be including the patients on all types of treatment for Parkinson's disease psychosis, including pimavanserin if it gets approved.

So that's already in plan to follow up the patients. We will be collecting more systematically AEs and SAEs, AEs of interest and SAEs, as well as quality of life and productivity data and caregiver burden. I just wanted to point out that.

DR. BRENT: Dr. Elmore, you had a comment.

MS. ELMORE: Yes. I was just going to comment that also the FDA stated earlier that there was inflammation, pulmonary inflammation seen in patients who had been treated long-term.

I'm sorry. Did you say that?

DR. FARCHIONE: Animals.

MS. ELMORE: Oh, in the animals, only in the

animals but not in people, no evidence of that.

Well, I think that what we've seen so far is that based on the studies as they've been done, we haven't seen any evidence that the animal studies translate to humans, and that's a really good thing. I think that's very promising, but I still think that it's something you'd want to keep in mind and consider going forward.

MS. BHATT: Before we go on to the question, we read the question again and vote, I'd like to remind everybody to please state your name for the record. It's important that we have your name for the record. Thank you.

DR. BRENT: I'm going to read the question. Has the applicant adequately characterized the safety profile of pimavanserin?

So I'm also going to read the procedures again. Please press the button on your microphone that corresponds to your vote. You will have approximately 20 seconds to vote. Please press the button firmly. After you've made your selection, the light may continue to flash.

If you're uncertain of your vote or you wish to change your vote, please press the corresponding button again before the vote is closed.

(Vote taken.)

MS. BHATT: The voting results for question 2 is yes, 11; no, 3; abstain, zero; and no voting, zero.

DR. BRENT: So we'll go around the room, and everybody can say what they voted and why. Dr. Elmore?

MS. ELMORE: Susan Elmore. I voted yes, and just for the reasons already stated. I feel that they've done an adequate job.

DR. SARKAR: Urmimala Sarkar. I voted yes. I was particularly convinced by the accumulated safety data from all four of their trials.

DR. GERHARD: Tobias Gerhard. I voted yes. Although I have quite a few concerns about the safety data, I think it's sufficient to move forward given the context of the drug as a whole.

But as I stated before, I think there would be significant postmarketing commitment advisable

to clarify the safety concerns, and I think observational methods are probably insufficient to do that. So some kind of simple trial for some of the severe effects and obviously a robust observational postmarketing program would be important.

DR. WINTERSTEIN: Almut Winterstein. I voted no for the exact reason. If they were adequately described, then we would not really come to the conclusion that a phase 4 commitment is needed. I think the data that are here require a phase 4 commitment. There is a statistically significant difference between the two treatment groups when serious adverse events are considered, and that looks too similar to what we have seen in the dementia population to not take seriously.

I agree with Dr. Gerhard that observational designs will be difficult in this framework, so a controlled trial, a phase 4 controlled trial, would clearly be the most adequate way to address this.

Given the large background incidence of mortality or serious adverse events, that wouldn't

require too many patients. And it would certainly allow those patients who are considering those medications to make an informed decision about risk/benefit, which I think right now, we clearly see with the discussions on numbers needed to treat and numbers needed to harm has still a very wide range. And whether a patient is willing to take the risk for a chance of death that is 1 in 10 or 1 in 100, to trade in hallucinations, this makes a huge difference.

So I think it's very important to have more data to allow everybody to make those decisions.

MS. MORGAN: I'm Linda Morgan, and I voted yes. And I am a patient, as you mentioned, and I would give the safety -- I mean, I voted yes, but with hesitation. I don't think it's black and white. And I think we need to take more data, consider more data long-term.

DR. SCHMID: Chris Schmid, and I voted no. I feel the numbers here are just really too small to make conclusions. As I raised the issue with the subgroups, I really don't know whether the

risks are higher in one group than another based on baseline severity. The death rate is fairly high in this group to begin with, but I don't know if it'd be elevated.

So the question asked whether I thought it had been characterized effectively, I just don't think I have enough information to make a decision.

DR. GRIEGER: Tom Grieger, and I voted yes to the question posed. I think we'll have more discussion when we get to the discussion of the risks versus benefits. I think they answered the question within the parameters of the protocol, the number of the patients they had in the study, the duration of time that they followed them.

MS. WITCZAK: Kim Witczak. I voted no, and I think it's back to the amount of data that we have.

DR. PICKAR: I voted yes, but I was concerned about the amount of data. It certainly was going through my mind, but I voted yes.

DR. BRENT: David Brent. I voted yes because I thought they adequately characterized the

safety and the numbers that they had. The numbers are small. I don't know going forward, if this ends up being approved, whether we need to indicate that there's a higher rate of serious adverse events in the drug than placebo.

To me, I'm voting yes because I thought they characterized it, but I think that that's something that should be part of the information that the public has in making their decision.

DR. IONESCU: Dawn Ionescu. I voted yes for very similar reasons to Dr. Brent and Grieger.

DR. NARENDRAN: Raj Narendran. I voted yes. I was skeptical, but I thought the FDA presentation of antipsychotics in dementia was very illuminating and felt like it wasn't any worse than the existing medications these patients are being put on. But there are some issues that need to be addressed going forward.

DR. FAHN: Stan Fahn. I did vote yes also, and I thought they looked at the key important side effect for this class of drugs, the antipsychotics. Does it worsen Parkinson's disease? I think they

did a good job looking at that. They didn't show any worsening. That was important.

Then, of course, they looked at all the other standard side effects, and I thought they covered everything pretty well. So I thought it was fairly adequate.

DR. DUDA: John Duda. I voted yes for similar reasons to Dr. Grieger. I thought given the patients that were exposed -- and keeping in mind that they presented the data for all the studies, not just the definitive of 020 trial, so I thought it was adequate.

DR. BRENT: I'm now going to summarize. Our group, the majority of us voted to indicate that the safety characterization was adequate. I think many of us were concerned about the small number, and that caused some of us to vote against that.

I think there was a strong endorsement that there should be some kind of postmarketing to try to determine the safety, especially compared to other agents that might be used for this condition.

I agree with Dr. Schmid that it looks like

there's a difference in the signal between different subgroups. The group with some evidence of dementia actually looked like the rate of serious adverse events was similar between drug and placebo and that that does need to be characterized better.

DR. TEMPLE: Can I just ask for a follow-up? There was something like 1200 patients exposed, which is not an untypical number. Is the concern people have that it wasn't long enough, that it wasn't controlled?

I heard some reference to the possibility of doing what I take to be a large long-term controlled trial in presumably these people. And I'd be interested in hearing whether people think that's a realistic possibility. It's not easy for me to imagine people in this condition entering such a trial against placebo. And entering it against another active drug will be uninformative, so that's not going to be very helpful.

So a little bit of discussion, I don't want to take hours, but a little discussion of this

would be helpful to us.

DR. BRENT: Dr. Grieger?

DR. GRIEGER: I think it's a great question. I mean, they did follow a large number of people in one way or another over time, but many of them weren't controlled. It was open label at that point in time. I don't know how tight the reporting was during that period of time.

Quite frankly, to the extent they reported it, it kind of glossed right over me compared to the data where they looked specifically at the placebo and the trial group and the control group during a specific period of time and reported the events.

So I think it's just a matter of the open-label component of that did not seem quite as rigorous. And I agree. I mean --

DR. TEMPLE: But it's not an accident the controlled trial only went 6 weeks. I doubt people would be willing be in for much longer, so then they crossed over to active drug because --

DR. GRIEGER: Right. But the other issue is

depending on the age of these people, looking at Medicare beneficiaries, something like two-thirds of them end up dying in a six-year period of time once they enter into the registry. So there is an issue with long-term trials in patients who have, for some of them, a very serious, potentially fatal disease of itself.

DR. BRENT: Dr. Winterstein?

DR. WINTERSTEIN: If I recall the numbers, there were roughly about 20 or 25 percent of patients who were on treatment, on other antipsychotic treatment, at study entry, so there was a fairly large population of patients who were not treated at study entry and who had had psychotic symptoms for a range of time.

So it doesn't seem that every single patient requires treatment immediately or makes a decision to get treated immediately.

DR. TEMPLE: Maybe you could do a comparator trial, but would that get you the answer you want to know? We already believe those drugs cause all kinds of problems, as the data you've seen already

shows. So if you did this and they were similar, what would you conclude? I don't know. It sounds like you really need a placebo or a no-treatment group.

Anyway, thanks for the discussion, though.

DR. BRENT: Dr. Sarkar?

DR. GERHARD: This is Toby Gerhard. I think it would still be important to see that this drug is not worse, which we certainly can't rule out. If we have an active comparator, given the background rates, I don't think it would have to be a long-term trial, and I don't think it would have to be a tightly controlled trial.

So a simple trial with a mortality outcome assessed after a relatively short period could be even 6 weeks, done in -- again, it could be an easy power calculation, but a thousand patients or so may be something that's doable and would be informative, for example, even against placebo for a short period or compared to quetiapine, which might be the most comparable.

I think that would be informative and would

certainly help us quantify the mortality risk that we're talking about. For some of the other obviously severe adverse effects, it becomes much more difficult because the outcomes assessment is so much harder.

DR. BRENT: Dr. Sarkar?

DR. SARKAR: I hope I don't get booted out the door for saying this, but I think a well-done observational study would actually add a lot. People are going to be using these drugs in the real world in a lot of different ways, and I think having some information about serious adverse effects and mortality just with real-world use in a larger, more diverse patient group would be very helpful.

DR. BRENT: Dr. Schmid?

DR. SCHMID: Yes, I would agree. I'm not even sure you need a placebo group here. I'm just looking at the data. Really, what was presented was there were 433 people in the 34-milligram group and the placebo group, and there's 3 deaths out of 124 in the 34-milligram group.

So that's about a 2 and a half percent death rate. And I just would like to know -- that's 3 times greater than what's in the placebo group. We all know what's happened with drugs that have gone on the market and then had to be pulled because the death rate goes up by 20 percent. We're talking about a 200 percent increase here potentially. I agree it's only 4 people.

So that was why I voted no because I just don't know whether that's real or not.

DR. BRENT: Thank you.

The third question is whether the benefits of pimavanserin for the treatment of psychosis outweigh the risk of treatment. Basically, the risk/benefit ratio. So we'll have discussion about that.

DR. GRIEGER: I think it would be helpful to perhaps categorize the patients that a physician would select for this medication, whether it includes using the SAPS-PD with a baseline score, or number of symptoms, or key symptom with a severity rating on it; not as a prescriptive

measure, but to just put that into the prescription guideline so that it isn't just a drug that you pull off the shelf when you pull the other ones off to give it a try.

I mean, it really should be people with a serious enough problem that you're willing to introduce a potential risk of an adverse event. I mean, we're supposed to do that all the time, but if you get people in primary care that are just throwing meds at something -- not to malign primary care, but there are people who sometimes prescribe these medications who have less experience with the subtleties of these medications and the long-term implications.

DR. DUDA: Just out of curiosity to the FDA, is there any precedent for a black box warning upon approval?

CAPT ANDREASON: Yes.

DR. DUDA: Sounds like a good option to me. I mean, honestly, that would take care of that problem.

DR. PICKAR: What would you suggest the

black box would say? How would you take a crack at that, John?

DR. DUDA: Oh, boy.

DR. PICKAR: Because I think it's an interesting thought.

DR. DUDA: I guess it would be similar to the black box warning for atypicals in dementia, suggesting that there's an increased risk of mortality.

DR. TEMPLE: Well, a question that we have to decide on -- and to my best knowledge, it has not been decided -- is whether the class box warning, which is given to all of them, whatever their particular nature, should also be applied to this. And I don't think we've decided that yet.

DR. BRENT: Dr. Sarkar?

DR. SARKAR: The way clinicians use black box warnings in the real world, at least for me as a clinician, I don't feel like I have enough data to say this needs -- I mean, the numbers are so tiny. It's just -- it doesn't feel meaningful enough to make such a large psychological barrier

for a clinician prescribing it. That's why I think we need more information.

DR. FAHN: Stan Fahn, and I just agree with you completely. I think it's still too small, and you need a longer surveillance period to see if this really holds up or not. I mean, as somebody mentioned earlier in the discussions this morning, that a one-number change would have made a big difference.

One other thing about this question, I pointed out earlier that there are some side effects that were more common in the placebo group than in the active drug treatment group. Are these flukes, or could there be something in this drug that has some benefits that we didn't know about in advance and it needs to be explored?

But I put that into the equation. Does the treatment with this drug outweigh the risks of side effects? And I think maybe this has to be put in the equation on the positive side as well. So keep that in mind when I look at this.

DR. BRENT: Ms. Witczak.

MS. WITCZAK: This is regarding the black box warning. I do think as a consumer that if it's a class-wide -- because if this does not have a black box warning on it, I can see it being out there and being promoted by the doctors that this might be another type of drug that does not have any of the side effects.

So I don't think it really adequately explains it because there are deaths that are associated, whether we have enough data or not. But if it's a class-wide, I think it's something to consider.

DR. BRENT: I just wanted speak to Ms. Witczak's comment, which is if you voted that there was enough data to determine the safety profile, then we have enough data to decide whether or not there should be a warning. If we're saying that we don't -- and we already voted. But to me, I feel like I voted at least to say that there was enough data to characterize the safety. But there is a signal that there are more serious adverse events and death in the group that got the drug,

and I think that that should be passed on to the consumer.

DR. TEMPLE: There is some class language that is not based on the data from the new submission. So antidepressants all say something about suicidality, antiepileptic drugs do, and it isn't because you have data for each new drug that confirms that. To me, the idea that 3 versus 1 somehow confirms the mortality finding is really at the outer edge.

But we do sometimes continue the class warnings. A new antipsychotic, for example, for conventional treatment, would ordinarily get the same box that all the rest of them do because of the accumulated data on the whole class, not because of in their trials they showed this, which they almost never would.

So anyway, we haven't decided on that, but we're going to think about that.

DR. BRENT: Dr. Duda?

DR. STONE: Yes. I didn't go into this in the talk, but all those drugs were these, except

for haloperidol, atypical antipsychotics. And haloperidol, while it still had very similar mortality rate, relative risk, the deaths in the haloperidol group were different. They were things like cancer, things that you would expect would be due to chance rather than something going on with the drug.

But we nonetheless decided to extend the warning to all the antipsychotics, not just the atypicals or second generation, in part, because we didn't want to imply that they were necessarily any safer.

Bob's right. If you have 3 deaths versus 1 here, it doesn't matter very much. You have a prior based on your -- and what we know about the antipsychotics, that 3 versus 1 is going to move that prior only very slightly. So it's still basically how relevant you think that our experience with these other antipsychotics in demented patients is to this drug.

DR. BRENT: Dr. Grieger?

DR. GRIEGER: I think it raised a very

interesting question. Are you going to classify this as an antipsychotic? My recommendation would be not because to class -- this goes back to what Dr. Pickar was saying earlier. If people view this as an antipsychotic, then it's free rein to use it on schizophrenia, bipolar with psychosis, depression with psychosis.

I wouldn't characterize it that way. It hasn't been proven that way. In fact, I think it's been looked at that way, and it's now being looked at a very specific way. So I think it's a unique drug, which may carry some of the risks of the other drugs, but it acts by a pretty different mechanism, a novel mechanism. And it's for a very novel population of people. That's all that it's been proven to work with. So I wouldn't class it as an antipsychotic because I think it would escalate the chance for misuse in the professional community.

I guess what I was getting at is something similar to -- and it wouldn't have to be, again, prescribed or proscribed if you didn't do it, but

something that says this drug has been proven to be effective in patients that are like this, this, this, and this, so that it just kind of lays out what is the population that you'd want to use this drug in: well, they've had Parkinson's disease for at least a year; well, they've had hallucinations for at least a month; well, these hallucinations are causing some kind of an impairment for them.

Whatever you-all work out with regard to the words, it should match what the study has been about, what kind of patients in what kind of setting.

DR. PICKAR: No surprise, I would agree with Tom on that part. The idea of labeling it an antipsychotic and that we're putting it in the category of those others, I think is a problem and hopefully not necessary.

It goes back to my earlier point about psychosis in drug-treated Parkinson's disease. It's a very specific thing with a very limited amount of data that we've seen. And I would have loved to have seen other data. It didn't show it

from other trials. So with this, I don't think it should be in that broad category.

DR. TEMPLE: Well, this has been very helpful, but we don't have to label it an antipsychotic to believe that the concern from those other drugs still applies. So those are somewhat separate questions, and we'll take all this into account.

Just to state the obvious, section 14, which describes the trials, is very good at giving who exactly was in the trials. Elements of that may or may not appear in the indication section. We don't like to make them too crowded. But that's a determination that's going to have to be made.

DR. SCHMID: I just had a point of clarification, back to the Mini-Mental. What percentage of the people were in those two groups? I don't recall whether you had those numbers.

DR. STANKOVIC: We'll bring that slide right up. There were about 50 people in the group that it was lower. Slide up, please.

There was in lower, yes, category of

Mini-Mental Status Exam versus 135 in the other.

DR. SCHMID: And this is in both studies?

DR. STANKOVIC: This is study 020, just the pivotal trial, yes.

DR. SCHMID: Okay. So the numbers you showed before, I think there were 12 serious adverse events -- greater than 25?

DR. STANKOVIC: We can project that again, yes.

DR. SCHMID: I'm just trying to figure out what the rate of --

DR. STANKOVIC: These numbers are very small, so it's --

DR. SCHMID: I know. I know. I'm just trying to figure out what the rate of adverse events was in that group.

DR. STANKOVIC: Slide up, please. So we had in patients of less than 25, we had 4 and 3 events in pimavanserin and placebo arm versus 8.5 versus 2.9 percent in pimavanserin versus placebo in patients with a Mini-Mental Status Exam above 25.

DR. SCHMID: So it's higher, but I agree the

numbers are small, so you don't really know if those are differences. Okay.

DR. STANKOVIC: Right, right.

DR. SCHMID: Thanks.

DR. BRENT: I'm going to re-read the third question. Do the benefits of pimavanserin for the treatment of psychosis outweigh -- wait a minute -- associated with Parkinson's disease outweigh the risk of treatment?

DR. TEMPLE: Associated with treated Parkinson's disease. I'm just trying to satisfy you.

DR. BRENT: Okay.

DR. DUDA: Sorry. John Duda. One last question. Can you give us some guidance on how the characterization of breakthrough therapy designation should impact this consideration of this question?

DR. FARCHIONE: I think that the issue of the breakthrough therapy, it's something that we assign to the development program. So it helps to get to this stage where we're talking about the

actual drug application more efficiently, sooner, whatever. But as far as the choice of whether the benefits outweigh the risks, it's the same as it would be for anything else.

DR. BRENT: Everyone vote now.

(Vote taken.)

MS. BHATT: The voting results, yes is 12; no is 2; abstain is zero; no voting is zero. And we'll go around the room, starting with Dr. Duda first. Please state your name for the record and why you voted.

DR. DUDA: John Duda. I voted yes for many of the comments I made before. I thought that given the -- it was proven effective, and the side effect profile, while somewhat concerning, is not convincing to me that it will stand up in larger numbers.

I think that from a movement disorder clinician perspective, I have plenty of patients who would tell me that they would gladly take a medication if they had moderate to severe psychosis in Parkinson's disease that had a 1 in 10 chance of

completely resolving their symptoms and if it had a 1 in 100 chance of killing them. They would still be happy to take it.

DR. FAHN: Stan Fahn. I voted yes. I think although the benefit is not as great as I would have liked, it's got some benefit. I think it may help a number of our patients, and we need something. This is a real big problem, and therefore, I voted yes.

I think the side effects presented don't outweigh the benefit, and the benefit outweighs the side effects. And that's why I voted yes.

DR. NARENDRAN: Raj Narendran. I voted yes for the above stated reasons.

DR. IONESCU: Dawn Ionescu. I voted yes as well. I just think especially for these disorders that are really difficult to treat where we have no options, many of these patients will say yes, I'm willing to take the risk. And I think, obviously, this question is going to need to be discussed with every patient that's started on this type of medication. But nonetheless, giving them something

that may help them for their severe disease is going to outweigh the risks for many of them.

DR. BRENT: David Brent. I also voted yes and for the same reasons. I was persuaded actually by the really terrible quality of life that these patients have. And I think as long as they can be given an informed choice about the risks, I think they ought to have the options.

DR. PICKAR: I voted yes as well. My concerns were already established, and Bob addressed them. And I'm just very pleased that we're going to hopefully help something get into -- treatment to help some of you folks out there and others folks who need it.

I think the concern around safety is real, and everyone is trying to do -- both to help people just to make sure that no one gets hurt by this. So I'm a yes.

MS. WITCZAK: Kim Witczak, no. And I'm for patients having treatments that are really beneficial that doesn't -- at the expense of safety. I'm not convinced with this one. I think

patients need to have all the information, and I'm just really concerned.

I'm in advertising. It's my background. I'm really concerned about how this is going to eventually going to get promoted into the PR, into the community. And I'm afraid of the other populations that will start using it off label.

DR. GRIEGER: Tom Grieger. I voted yes for the reasons already outlined by others.

DR. SCHMID: Chris Schmid. I voted yes with some reservations. I think the need here outweighs the potential risk, which I really, as I voted no, can't even characterize that. So I guess I'm hoping that the risks are going to be small, and I think the benefits for some of these people who are very sick and whose families are affected by this, I think they're probably willing to take that risk.

MS. MORGAN: Linda Morgan. I voted no because of all the discussion of this.

DR. WINTERSTEIN: Almut Winterstein. I voted yes. If there were a safe and effective alternative on the market, I would not have voted

yes. But I think that, in particular, the public hearing today was very compelling. There clearly is a need.

I agree with Dr. Brent that patients need to be able to make an informed decision. I think right now with the data they have, they cannot. So I would very much recommend that the FDA does consider a phase 4 study to allow patients to make that decision.

DR. GERHARD: Tobias Gerhard. I voted yes as well for the reasons that were stated before. Definitely have some concerns about the safety. I think it is generally a slippery slope to compare the harms of a medication to be approved for a condition where there aren't a lot of alternatives, or any alternatives, with unapproved alternatives that people use.

But I think in this situation, it is somewhat justified because, clearly, the antipsychotics and the second generation antipsychotics are used very widely. And clearly, it is, in my perception, almost standard of

practice to do so.

So in that sense, I think there is merit to make that comparison to that class of drugs that clearly comes with its own established safety concerns. So in that context, I think it's a yes, though we need a robust postmarketing program for this drug.

DR. SARKAR: Urmimala Sarkar, I voted yes with the plea to the FDA to please consider a large observational study so we can ensure that once it goes into real-world use, that the benefits will outweigh the risks.

MS. ELMORE: I'm Susan Elmore. I voted yes, and I don't think that this drug is the golden egg for Parkinson's disease psychosis. There are certainly some risks in terms of SAEs and even death. But importantly to me, in this study, there were no underlying mechanisms, no unifying mechanisms that could link them all. And that was important to me.

Also importantly is that it does not worsen the symptoms of Parkinson's disease. And

obviously, we've already stated, no currently available effective treatment for Parkinson's disease psychosis that won't block dopamine receptors.

So for me, there was a clear need for such a drug, and the benefits did outweigh the risks for this particular group of patients.

DR. BRENT: So I will summarize now. I would say that even the people that voted yes did so with qualifications. There's concerns about the safety and emphasis that the FDA should be as specific as possible in the labeling of the drug, that to try and do what we can to prescript off-label use.

But given the lack of alternatives and the poor quality of life of this condition, I think that explained the majority of people endorsing the favorable risk/benefit ratio.

I have one last thing to read, or two last things. Before we adjourn, are there any last comments from the FDA?

DR. UNGER: Thanks. I'm Ellis Unger. I'm

director of Office of Drug Evaluation I.

One of the issues, one of the places I had hoped someone would go, but no one went there, is that in the evaluation of benefit and risk, one of the critically important aspects is whether an individual patient can figure out if they're deriving benefit from the drug that they're taking.

So sometimes if we put a stent in somebody's coronary arteries, we say here, take this anti-platelet drug for the rest of your life. Good luck. The patient just takes it and is subjected to whatever the risk is.

My question is whether an individual patient who has psychosis associated with Parkinson's disease could take the drug and figure out that they're feeling better, that they're having fewer hallucinations, less problem, and continue the drug; whereas the person who feels like I'm not really feeling any better would know that, because if they know that, they can stop the drug. And that really enhances the benefit/risk relationship of the drug.

So for the people around the room who treat patients with this disease, I'm just wondering if they think an individual patient can figure out if they are feeling better if they're taking the drug.

DR. DUDA: John Duda. Certainly, from my experience with the other atypical antipsychotics, that's the case. We often start out at a very low dose of quetiapine, for example, and ask the patient, and maybe importantly, the caregiver, if they see a difference in behavior. And often, they do. Sometimes they don't, in which case we kind of titrate the dose effectively.

So it is possible based on patient and caregiver personal perspective of the efficacy to even titrate the dose. Obviously, this won't have a dose titration, I guess, but we use that clinically.

DR. FAHN: Stan Fahn. Let me also add to that that let's say we did add a little bit of quetiapine, and the drug works, they're better. And for a period of time, maybe six months, a year or so, everybody is fine, we would talk with the

patient and the caregiver and with the physician, of course, and we'd discuss how about coming off and see how they do. And that's very common.

So we do that, and if they have symptoms again, we reintroduce it.

DR. UNGER: Ellis Unger again. So still, something we sometimes put on the label, reassess how well you think the patient is doing and reassess the need for the drug. And maybe that could help mitigate some of the concerns around the room about the safety. I see people shaking heads.

DR. BRENT: Ms. Witczak?

MS. WITCZAK: I was just going to say, how many people -- will it go to the GPs and the internists? Because that's one of the things that I think a lot of times, with a lot of these medications, they do go into the physician thinking that it's themselves and the disease. And physicians are often not able to identify that it's the treatment drug that's causing it.

So I think that is a big concern, especially when you get into the GPs.

DR. BRENT: Are there any additional comments?

DR. GRIEGER: I guess I'd ask the neurologists in the room what -- I mean, from my sense as a psychiatrist, even though I've got some training in neurology, I wouldn't feel comfortable in managing these patients by myself.

Do you find general practice, internists, that just feel comfortable adjusting doses without consulting with you-all?

DR. FAHN: I think most neurologists get some training from specialist movement disorders during their training program, residency, and also the CME courses. Internists, I think, are uncomfortable once they get any complications from a Parkinson's drug, a little bit dyskinesia is wearing off, and they don't want to touch them anymore, and they send the patients to the neurologists. And many neurologists will send them to a movement disorder specialist because of the same problem.

It becomes very sophisticated. I should

point out to everybody, Parkinson's disease is a very complex disorder. We already heard about the motor, non-motor, but it's also difficult in the treatment. These drugs do all kinds of things -- the drugs we use to help the patients do all other kinds of problems, and we just discussed one of them today.

This is a much more complicated disease than we anticipated, and even the movement disorder specialists are having a hard time getting a grasp on how to best to do. We still don't know when it's best to start levodopa. After all these years, what, 40 years or 50 years of levodopa, should we start right away, should we delay it? This is still an unanswered question.

So it's an evolving thing. It's part art, part science. So I think many doctors won't feel comfortable handling this and would send it to a specialist.

DR. BRENT: Dr. Sarkar?

DR. SARKAR: I'm actually a general internist, and I practice in a setting where there

aren't very many subspecialists. But I would say that titrating Parkinson's medications is solidly in the purview of a specialist.

Adjournment

DR. BRENT: If there are no other comments, then I'd first like to thank everybody for their participation, and we'll now adjourn this meeting.

Panel members, please take all your personal belongings with you as the room is cleaned at the end of the meeting day. All materials that are left on the table will be disposed of. Please remember to drop off your name badge at the registration table on your way out so they may be recycled. Thanks again.

(Whereupon, at 3:49 p.m., the meeting was adjourned.)