FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

PSYCHOPHARMACOLOGIC DRUGS ADVISORY COMMITTEE MEETING (PDAC)

Virtual Meeting

Friday, June 17, 2022

8:45 a.m. to 3:05 p.m.

Meeting Roster

DESIGNATED FEDERAL OFFICER (Non-Voting)

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Division of Advisory Committee and

Consultant Management

Office of Executive Programs, CDER, FDA

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C O N T E N T S

C O N T E N T S (continued)

P R O C E E D I N G S

(8:45 a.m.)

Call to Order

DR. NARENDRAN: Good morning and welcome. I would first like to remind everyone to please mute your line when you are not speaking. For media and press, the FDA press contact is April Grant. Her email and phone number are currently displayed.

My name is Raj Narendran, and I will be chairing this meeting. I will now call the June 17, 2022 Psychopharmacologic Drugs Advisory Committee Meeting to order. Dr. Joyce Frimpong is the designated federal officer for this meeting and will begin with the introductions.

Introduction of Committee

DR. FRIMPONG: Good morning. My name is Joyce Frimpong, and I'm the designated federal officer for this meeting. When I call your name, please introduce yourself by stating your name and affiliation.

Dr. Robert Baker?

DR. BAKER: Good morning. This is Robert

Baker. I'm the deputy chief medical officer at Eli Lilly and Company, so I'm the industry representative.

DR. FRIMPONG: Dr. Walter Dunn?

DR. W. DUNN: Hi. This is Walter Dunn, assistant clinical professor at UCLA and the Greater Los Angeles VA.

DR. FRIMPONG: Dr. Jess Fiedorowicz?

DR. FIEDOROWICZ: Yes. Hello. This is Jess Fiedorowicz, professor at University of Ottawa.

DR. FRIMPONG: Dr. Satish Iyengar?

DR. IYENGAR: My name is Satish Iyengar. I'm from the University of Pittsburgh, where I am professor and chair of the statistics department.

DR. FRIMPONG: Dr. Sonia Krishna?

DR. KRISHNA: Good morning. This is Dr. Sonia Krishna. I'm affiliate faculty at UT Austin, Dell Medical School.

DR. FRIMPONG: Dr. Rajesh Narendran?

DR. NARENDRAN: Hi. This is Raj Narendran. I'm a psychiatrist at UPMC, professor of psychiatry and radiology at the University of Pittsburgh

Medical Center.

DR. FRIMPONG: Ms. Kim Witczak?

MS. WITCZAK: Good morning. Kim Witczak, Woodymatters, a drug safety organization out of Minneapolis.

DR. FRIMPONG: Dr. Liana Apostolova?

DR. APOSTOLOVA: Good morning. This is Liana Apostolova. I am the Barbara and Peer Baekgaard Professor in Alzheimer's Disease Research, and professor in neurology from Indiana University.

DR. FRIMPONG: Dr. Merit Cudkowicz?

DR. CUDKOWICZ: Hi. Merit Cudkowicz. I am chair of neurology at Mass General Hospital and professor of neurology at Harvard Medical School.

DR. FRIMPONG: Dr. Dean Follmann?

DR. FOLLMANN: Yes. Hi. I'm Dean Follmann, head of biostatistics at the National Institute of Allergy and Infectious Diseases.

DR. FRIMPONG: Ms. Colette Johnston?

MS. JOHNSTON: Colette Johnston. I'm a patient advocate and caregiver.

DR. FRIMPONG: Dr. Madhav Thambisetty?

DR. THAMBISETTY: Good morning. This is Madhav Thambisetty. I'm a senior investigator at the National Institute of Aging and chief of the clinical and translational neuroscience section. I'm also an adjunct professor of neurology at the Johns Hopkins School of Medicine.

DR. FRIMPONG: Dr. Billy Dunn?

DR. B. DUNN: This is Dr. Billy Dunn. I'm the director of the Office of Neuroscience at the FDA.

DR. FRIMPONG: Dr. Tiffany Farchione?

DR. FARCHIONE: Hi. This is Tiffany Farchione. I'm the director of the Division of Psychiatry at FDA.

DR. FRIMPONG: Dr. Bernard Fischer?

DR. FISCHER: Hi. This is Bernie Fischer. I'm the deputy for psychiatry at the FDA.

DR. FRIMPONG: Dr. Paul Bossie?

DR. BOSSIE: Hi. I'm the clinical reviewer at the Division of Psychiatry for the FDA.

DR. FRIMPONG: And Dr. Xiang Ling?

DR. LING: Hi. This is Xiang Ling, the statistical reviewer at the FDA.

DR. NARENDRAN: For topics such as those being discussed at this meeting, there are often a variety of opinions, some of which are quite strongly held. Our goal is that this meeting will be a fair and open forum for discussion of these issues and that 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 members of the media are anxious to speak with the FDA about these proceedings, however, 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.

Dr. Joyce Frimpong will read the Conflict of Interest Statement for the meeting.

Conflict of Interest Statement

DR. FRIMPONG: 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 of 1972. With the exception of the industry representative, all members and temporary voting members of the committee are special government employees 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 conflict of interest laws, covered by but not limited to those found at 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 is determined that the agency's need for a special government employee's services outweighs his or her potential financial conflict of interest, or when the interest of a regular federal employee is not so substantial as to be deemed likely to affect the integrity of the services which the government may expect from the employee.

Related to today's discussion, 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 employers. These interests may include investments; consulting; expert witness testimony; contracts, grants, CRADAs; teaching,

speaking, writing; patents and royalties; and primary employment.

Today's agenda involves the discussion of supplemental new drug applications 210793-008 and 207318-011, efficacy supplement resubmission for Nuplazid, pimavanserin, tablets, submitted by Acadia Pharmaceuticals, Incorporated, for the proposed treatment of hallucinations and delusions associated with Alzheimer's disease psychosis. This is a particular matters meeting during which specific matters related to Acadia Pharmaceuticals, Incorporated supplemental new drug applications will be discussed.

Based on the agenda for today's meeting and all financial interests reported by the committee members and temporary voting members, a conflict of interest waiver has been issued in accordance with 18 U.S.C. Section 208(b)(1) to Dr. Walter Dunn. Dr. Dunn's waivers include stock holdings in four competing firms. The aggregate market value of his financial interest in the common stock of the four firms is between $17,500 and $37,500. The waiver

allows Dr. Dunn to participate fully in today's deliberations. FDA's reasoning for issuing this waiver are described in the waiver document, which is posted on FDA's website.

A copy of the waiver may also be obtained by submitting a written request to the agency's Freedom of Information Division, 5630 Fishers Lane, Room 1035, Rockville, Maryland, 20857, or requests may be sent via fax to 301-827-9267.

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 FDA's invited industry representative, we would like to disclose that Dr. Robert Baker is participating in this meeting as a non-voting industry representative, acting on behalf of regulated industry. Dr. Baker's role at this meeting is to represent industry in general and not any particular company. Dr. Baker is employed by Eli Lilly and Company.

We would like to remind members and

temporary voting members that if 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. NARENDRAN: We will proceed with the FDA's opening remarks from Dr. Tiffany Farchione.

FDA Opening Remarks – Tiffany Farchione

DR. FARCHIONE: Good morning, and welcome to the Psychopharmacologic Drugs Advisory Committee meeting. My name is Tiffany Farchione, and I'm the director of the Division of Psychiatry here at FDA. Today, we will be discussing Acadia Pharmaceuticals' supplemental new drug application for pimavanserin for the treatment of hallucinations and delusions associated with Alzheimer's disease psychosis.

The application under review here is a resubmission after a complete response action. In other words, the agency reviewed and did not approve a previous version of this application. I want to emphasize that the committee should not assume that the prior action reflects the agency's position on the current application.

The applicant was previously seeking a general indication for the treatment of all dementia-related psychosis, regardless of the underlying disease responsible for dementia, but the current application has narrowed the proposed indication for the treatment of Alzheimer's related psychosis and has submitted a number of new analyses in an attempt to address the concerns outlined by the agency with the earlier decision.

There are no new studies with this submission, but the agency has agreed to consider the additional analyses in the context of the indication the sponsor now seeks. It's important to acknowledge that the applicant's resubmission for this revised indication focused only on

Alzheimer's disease and was discussed with us in multiple presubmission meetings, and we prospectively agreed that their current approach was reasonable and reviewable.

Today, our team's presentations will briefly describe the regulatory history, including relevant aspects of the complete response decision and post-action discussions with the applicant, followed by our evaluation of the current application.

The applicant is now seeking an indication for the treatment of hallucinations and delusions associated with Alzheimer's disease psychosis. Alzheimer's disease is the most common form of dementia in the United States. The latest estimate puts its prevalence at 6.5 million individuals. The pathological hallmarks of Alzheimer's disease include extracellular deposits of amyloid beta, known as plaques, and intracellular aggregates of hyperphosphorylated tau or neurofibrillary tangles.

Although cognitive decline is the predominant symptom, neuropsychiatric symptoms,

including hallucinations and delusions, are common and severe. These neuropsychiatric symptoms cause profound distress for patients and their caregivers, are severely debilitating, and are associated with a higher risk of rapid progression to severe dementia, death, and out-of-home placement.

I think that I advanced one too early. I apologize.

Currently, there are no approved pharmacologic treatments for hallucinations and delusions associated with Alzheimer's disease psychosis. Off-label use of antipsychotic medications approved for other conditions occurs, however, the American Psychiatric Association practice guideline on the use of antipsychotics to treat agitation or psychosis in patients with dementia notes that the benefits of antipsychotic medications are small at best. There is a significant and pressing unmet need for the treatment of hallucinations and delusions associated with Alzheimer's disease psychosis.

Pimavanserin, the product currently under review, is a serotonin-selective inverse agonist that preferentially targets the 5-HT2A receptor subtype. It is an approved product indicated for the treatment of hallucinations and delusions associated with Parkinson's disease psychosis or PDP. With the current submission, the applicant is seeking a second indication, this time for the treatment of hallucinations and delusions associated with Alzheimer's disease psychosis or ADP.

The applicant cites three sources of evidence to support this new indication. First, the prior approval of pimavanserin for the treatment of hallucinations and delusions associated with PDP, making the case that ADP and PDP are closely related conditions. Second, Study 019, which was a phase 2, 12-week, double-blind, placebo-controlled study in subjects with Alzheimer's disease psychosis. The primary endpoint in this study was the change from baseline to day 43 on the Neuropsychiatric Inventory Nursing

Home Version Psychosis Score, and the study was positive on the prespecified primary endpoint. And finally, Study 045, which was a phase 3 relapse prevention study, comprising a 12-week, open-label period, followed by a 26-week randomized withdrawal, double-blind period. This study included subjects with multiple subtypes of dementia, including a large Alzheimer's disease subgroup. The primary endpoint was time from randomization to relapse in the double-blind period, and the study was positive, based on the prespecified primary endpoint.

A note on the approved indication, the prior approval on PDP was based on Study 020, a phase 3, randomized, double-blind, placebo-controlled, 6-week study of pimavanserin versus placebo in subjects with Parkinson's disease and psychosis that developed after the diagnosis of Parkinson's.

Of the 185 subjects in the intention-to-treat analysis set, 46 had an MMSE score less than 25 and were considered a Parkinson's disease dementia subset. The primary

endpoint was the change from baseline to day 43 on the Scale for Assessment of Positive Symptoms Parkinson's Disease, or SAPS-PD, total score, which is a 9-item scale derived from the 20-item SAPS Hallucinations Plus Delusions, or SAPS-H+D, subscales. The study was positive on its prespecified primary endpoint.

For the current submission, the applicant presented Study 019 as the primary evidence to support the Alzheimer's disease psychosis indication. Although the agency raised concerns about the design and conduct of this study in the complete response letter to the original submission, the applicant has successfully addressed these concerns with this submission. As previously noted, the study was positive on the primary endpoint at day 43. The agency seeks the committee's input on the overall persuasiveness of the data from Study 019.

The applicant presents Study 045 as additional supportive evidence. This study was positive on the prespecified primary endpoint in a

population consisting of subjects with several dementia subtypes. Primary endpoint results by dementia subgroup were strongest in subjects with Parkinson's disease dementia or PDD. The applicant has conducted a series of post hoc analyses intended to show that pimavanserin's effect in the ADP subgroup is consistent with that in the PDD subgroup.

As previously noted, the applicant is citing the prior approval of pimavanserin for the treatment of hallucinations and delusions associated with Parkinson's disease psychosis as evidence to support this application. It is common for companies to seek additional related indications following an initial approval. The agency considers that related initial indication as a source of evidence for subsequent supplemental applications, so often requires only a single additional study in the new population. The applicant asserts that ADP and PDP should be considered closely related conditions.

The design of Study 045 was based on the

a priori assumption that this approach was reasonable, and the agency agreed with that approach. Although there are differences in the pathophysiology of Alzheimer's and Parkinson's disease, psychotic symptoms are present in both. However, the physiological underpinnings of psychosis in each condition are unknown. Nonetheless, the efficacy of pimavanserin in Parkinson's disease psychosis contributes to a prior expectation of benefit in a related condition such as Alzheimer's disease psychosis.

On face, the subgroup results of Study 045 may suggest differences in treatment response; however, the successful outcome of Study 019 may also suggest that these observed subgroup differences in Study 045 are not indicative of a lack of efficacy in Alzheimer's disease psychosis.

The issues I've outlined thus far are all related to the evidence supporting effectiveness. Safety will not be a focus of today's discussion. The findings from the supplemental new drug application development program are largely

consistent with the known safety profile of pimavanserin, and we do not have any concerns related to safety that would preclude approval.

So the charge to the committee today is to discuss the evidence supporting the effectiveness of pimavanserin for the treatment of hallucinations and delusions in Alzheimer's disease psychosis, including the strengths, limitations, and potential contribution of Study 019, Study 045, and the prior approval of pimavanserin for the treatment of hallucinations and delusions associated with Parkinson's disease psychosis.

Following that discussion, we will ask for your vote on the question, does the available evidence support a conclusion that pimavanserin is effective for the treatment of hallucinations and delusions in Alzheimer's disease psychosis. Thank you.

(Pause.)

DR. NARENDRAN: I apologize. There's another section I have to read.

Both the FDA and the public believe in a

transparent process for information gathering and decision making. To ensure such transparency at the advisory committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages all participants, including the applicant's non-employee presenters, to advise the committee of any financial relationships that they may have with the sponsor such as consulting fees, travel expenses, honoraria, and interest in the sponsor, including equity interests and those based upon the outcome of this meeting.

Likewise, 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 presentations from Acadia Pharmaceuticals.

Applicant Presentation – Daryl DeKarske

MR. DeKARSKE: Members of the Psychopharmacologic Drugs Advisory Committee and members of the FDA, my name is Daryl DeKarske, and I'm the head of Regulatory Affairs and Translational Sciences at Acadia. Thank you for the opportunity to introduce the pimavanserin development program supporting our resubmission application for pimavanserin for the treatment of hallucinations and delusions associated with Alzheimer's disease psychosis.

Unlike currently available multireceptor acting antipsychotic drugs that primarily act by dopamine receptor blockade, pimavanserin selectively targets serotonergic 5-HT2A receptors as an inverse [inaudible – audio gap].

Acadia studied pimavanserin for the potential to treat psychosis in patients with Parkinson's disease, or PDP, without adversely impacting their motor function, a core symptom of Parkinson's disease. This profile was demonstrated in a phase 3 study in patients with PDP, and based

on these results, the FDA granted pimavanserin a breakthrough therapy designation.

In April 2016, FDA approved pimavanserin 34 milligrams once daily for the treatment of hallucinations and delusions associated with PDP under the trade name Nuplazid. Today, we'll discuss the data supporting a proposed indication for pimavanserin 34 milligrams once daily for the treatment of the hallucinations and delusions associated with Alzheimer's disease psychosis or ADP.

Evidence of pimavanserin's effectiveness for the newly proposed ADP indication comes from three independent placebo-controlled clinical studies: Positive Study 019, which demonstrated a clinically meaningful benefit in patients with ADP; confirmatory evidence of effectiveness from Positive Study 020 in patients with PDP, a closely related indication, and Study 020 was the basis of the FDA approval of pimavanserin for the treatment of PDP, and the pimavanserin treatment effect in ADP patients will be evidenced in the presented

clinical study data as being consistent with that observed in PDP patients; and supportive evidence from Positive Study 045 in patients with dementia-related psychosis, or DRP, in which pimavanserin-treated patients showed a highly statistically significant reduction of risk of psychosis relapse.

Patients with ADP [inaudible – audio gap] -- subgroup evaluated, and although not statistically significant, showed a clinically meaningful reduction in the risk of psychosis relapse. We also saw consistent evidence of efficacy across multiple support of analyses in the ADP subgroup.

Relevant FDA guidance states that effectiveness can be established by one adequate and well-controlled clinical study in a new indication for an approved drug supported by confirmatory evidence that comes from existing adequate and well-controlled clinical study data that demonstrated the effectiveness of that same drug for another closely related approved

indication.

Historical context helps to put into perspective the path taken for the proposed ADP indication. Shortly after the approval of pimavanserin for PDP, Positive Study 019 [inaudible] results in patients with ADP became available. Importantly, we also observed that pimavanserin's treatment effect did not negatively impact a core symptom in these Alzheimer's disease patients' cognition.

Acadia aligned with the FDA on a development plan to support a broad indication for the treatment of DRP, specifically a randomized withdrawal Study 045. The goal of Study 045 was to demonstrate pimavanserin's efficacy for treating psychosis regardless of the underlying dementia diagnosis, consistent with the clinical understanding of overlapping pathology and psychotic symptoms among dementia subgroups. The study design also had the benefit of mimicking the way patients with DRP are treated in the real world. It would limit the duration of potentially

ineffective therapy and would also assess pimavanserin's maintenance of efficacy.

The primary analysis evaluated risk of relapse in the overall DRP population. The percentage of patients among the dementia subgroups was targeted to be representative of their epidemiological prevalence. As a result of a prespecified interim efficacy analysis that showed a highly statistically significant reduction of the risk of relapse, the independent data monitoring committee recommended stopping Study 045 early. Acadia shared the study results with FDA at a [inaudible].

In April 2021, FDA's complete response letter described concerns regarding a potential differential pimavanserin treatment effect among the dementia subgroups in Study 045. Although the study was not designed to evaluate the risk of relapse in individual dementia subgroups, a robust treatment effect in the Parkinson's disease dementia subgroup was noted, along with a lack of statistical separation in the other dementia

subgroups. Concerns regarding the design and conduct of Study 019 were also raised.

Following the complete response letter, Acadia presented to FDA sensitivity analyses for Study 019 that confirmed the primary endpoint conclusions, as well as the consistency of treatment effect observed in Study 020. We note that FDA has indicated in their briefing document that Study 019 was designed with features that could allow it to be considered adequate and well controlled, and that the sensitivity analyses Acadia conducted would allow for FDA to rely on the data for regulatory decision making.

With respect to Study 045, Acadia also presented to FDA new analyses that supported both a consistent and clinically meaningful pimavanserin treatment effect across the dementia subgroups, including in the ADP subgroup. Further, these analyses indicated a basis for their robust findings in the Parkinson's disease dementia subgroup. FDA expressed a readiness to review a resubmission in support of a treatment of ADP

indication, and in February of this year, Acadia resubmitted.

The pimavanserin clinical study efficacy data we provided in our resubmission, and which we will present today, demonstrate that pimavanserin is a [inaudible], and the risk of relapse, according to multiple clinical studies and measures, without adversely [indiscernible] impacting cognition or motor function.

Importantly, since the approval [inaudible] of pimavanserin for the treatment of PDP, an expanded clinical safety data set is now available and corroborates a favorable and differentiated safety profile. Further, six years of Nuplazid postmarketing experience and greater than 44,000 patients with PDP provides continued reassurance of its favorable safety profile. Although safety is not a focus of today's meeting, it is important to consider pimavanserin's differentiated safety profile to inform the overall positive benefit-risk in the context of the current treatment landscape and high unmet medical need of

patients with ADP.

You will hear later in our presentation how much distress psychosis can cause patients with ADP and the result in accelerated nursing home placement and increased risk of morbidity and mortality. Unfortunately, there remains no FDA approved treatment for patients with ADP. While Nuplazid is the only drug approved in the U.S. to treat PDP, payors require a strict diagnosis of PD for insurance coverage. Consequently, we see virtually no off-label prescriptions for uses outside of PDP.

Today, healthcare providers are left to consider off-label use in available multireceptor acting antipsychotics, which have not demonstrated efficacy in ADP and are associated with potentially serious safety issues, including adverse impacts on cognition and motor function.

With this introduction in mind, here is the agenda for our presentation. Dr. Tariot will discuss the urgent unmet medical need for effective treatment of patients with ADP. Dr. Ballard and

Dr. Hendrix will describe the pimavanserin clinical study efficacy results, as well as the supportive analyses across these studies. Dr. Turner will then briefly review key aspects of pimavanserin's safety profile; and Dr. Stankovic will present the benefit-risks in [indiscernible – audio gap].

I will now invite Dr. Tariot to review the unmet medical need.

Applicant Presentation – Pierre Tariot

DR. TARIOT: Thank you. Good morning. I'm Pierre Tariot. I'm an internist and geriatric psychiatrist, and director of the nonprofit Banner Alzheimer's Institute. I was also closely involved in the 045 trial, the randomized withdrawal study in dementia-related psychosis.

It's a privilege to speak with you today to share some of the background on Alzheimer's disease psychosis and the current unmet need that these patients, their families, and their loved ones face. I have been caring for and studying patients with Alzheimer's disease and other dementias for more than 30 years, and I can tell you very simply

that if left untreated, psychosis has significant and sometimes devastating consequences for our patients; but as you heard, there are no approved treatments for Alzheimer's disease psychosis, and current off-label options are woefully inadequate and often cause [inaudible].

Let me begin with a little level setting. Quote, "Dementia is a common clinical syndrome that involves crippling cognitive impairment and adverse effects on social, occupational, and even basic aspects of functioning." Dementia affects at least 7.9 million Americans and, as you've heard, there are various subtypes of dementia, with Alzheimer's being the most common, accounting for nearly 70 percent of cases.

The other common forms of dementia are vascular dementia, Lewy bodies dementia, Parkinson's disease, and frontotemporal dementia. Bear in mind that the different dementias can have overlapping pathologies, including Alzheimer's and Parkinson's disease, and that older persons with advanced dementia can have more than one pathology.

So these conditions are closely related to one another, and my own experience conforms with the epidemiological data.

Next, neuropsychiatric signs [inaudible] at some point in the course of illness, although their frequency time to onset, pattern, and severity do vary from patient to patient. Among these neuropsychiatric features, psychosis is particularly important. This term refers specifically to hallucinations or delusions, which occurs secondary to the underlying disease.

Now let's focus just on Alzheimer's. About 30 percent of these patients experience psychosis at any given time. This psychosis injures with generally waxing and waning symptoms that gradually increase in severity over time, leading to loss of independence, as well as increased distress and burden to the patient, the family, and caregivers.

The distortion of reality, a core feature of psychosis, can further compound the disorientation that patients experience as their cognitions declines, leading to further distress. These and

other neuropsychiatric signs and symptoms also lead to decreased quality of life, and as you've heard, earlier progression to nursing home care, severe dementia, and even death.

The takeaway is that there is a close relationship between the clinical manifestations of Alzheimer's disease psychosis and morbidity, and mortality. However, despite this close relationship, as you've heard, there are currently no approved drugs in the U.S. for the treatment of patients with Alzheimer's disease psychosis.

Now, moving on to management, it's considered best practice to begin with non-pharmacological interventions, which I do always attempt. But such methods fail commonly, leaving us clinicians with little choice other than to deploy pharmacological interventions; namely antipsychotic agents.

Based on clinical indications, antipsychotic agents are used for patients whose symptoms are frequent, severe, dangerous, and cause significant distress. One review of Medicare claims data from

2008 to '16 showed that roughly two-thirds of patients with dementia-related psychosis were prescribed an antipsychotic off label. But these agents come with significant limitations. Imagine feeling that you must choose a medication with limited [indiscernible] efficacy at best, and an 80 to 90 percent chance of toxicity because there are no alternatives.

The toxicities are due, in part, to the blockade of dopaminergic, histaminergic, and muscarinic receptors contributing to cognitive impairment and increased mortality, among many other adverse effects. Let me briefly discuss the risk-benefit data for these agents.

To highlight an example of the limited efficacy and high discontinuation rate we see with atypical antipsychotics, I show here the key findings from the CATIE-AD trial published in the New England Journal. It was the largest NIH-funded, randomized, placebo-controlled trial of the effectiveness of atypical antipsychotics for psychosis, agitation, and aggression in persons

clinically diagnosed with Alzheimer's disease.

Three antipsychotics and placebo were compared. There were no significant differences among treatments with regard to time to discontinuation of treatment for any reason, which was the primary [indiscernible] outcome, shown on the left here. Likewise, a key secondary outcome, the time to discontinuation of treatment due to adverse event, intolerability, or death, favored placebo, as shown on the right.

Together with Dr. Lon Schneider, I was the co-principal investigator of the study, as well as the site principal investigator. The first patient that I enrolled was an aged woman being cared for at home by her son. She gradually developed a fixed and increasingly frightening delusion that he was going to harm her. This came to a crisis one day when she pushed him through a plate glass window and attacked him with a fireplace poker. The ambulance brought her to our clinic at the family's request.

This case is not an exaggeration; it is an

example of what clinicians, patients, and families in the real world are struggling with. This is why we sometimes feel that we have no choice but to prescribe atypical antipsychotics, but you can see how limited their effectiveness is.

The CATIE-AD study also showed that these drugs were associated with significant decline in cognition, shown by worsening on the Mini-Mental Status Examination. The participants on drug declined an average of 2.4 points more than those on placebo over the 6-week study, equivalent to the decline typically seen over one year in dementia. I also want to point out that treating physicians in the trial were likely to switch medications quickly due to lack of efficacy or to adverse effects.

So as this trial illustrates, despite the hope that [indiscernible] antipsychotic drugs would be more [inaudible] their use, only a small fraction of patients had both benefit and few or no side effects. The data from this study illustrate what's seen in the rest of the literature

[inaudible] high.

In addition, antipsychotic drugs increased the risk of death in elderly patients with dementia-related psychosis. The mortality data here comes from the 2005 meta-analysis by Lon Schneider and colleagues, showing increased risk in all-cause mortality. [Inaudible].

The FDA had previously conducted its own meta-analysis and came to the same conclusion. These pronounced negative impacts of [inaudible] and cognitive function are reflected in product labeling, as well as our use in clinical practice.

[Indiscernible], the American Psychiatric Association guidelines recommend judicious use of antipsychotics when non-pharmacological therapy alone has been effective. An individualized treatment plan involving a full discussion of benefits and risks is developed with each patient and family. The medication is started off label, and if no significant response is seen after 4 weeks, it's to be withdrawn. Even if the patient does respond, we make the decision with the patient

and family to attempt to taper and ideally withdraw the medication as soon as possible because of its known toxicities, hopefully within 4 months of treatment initiation.

So this is the clinical context for today's presentation. We constantly are faced with the predicament of not treating patients who are desperately in need [inaudible] -- and marginal, noting the APA, marginal efficacy at best -- [indiscernible] available and highly problematic options. Their condition is serious, and the symptomatic consequences can be life altering.

Effective and safe treatment of these symptoms means relief of distress, restoration of dignity, and allowing our patients to remain home instead of being institutionalized. This is what is at stake. It would be [inaudible] of our patients and their families, even to the healthcare system at large, in that therapeutic option [inaudible] efficacious, if not more so, than available antipsychotics, and one that was not

associated with their significant toxicities. It would also be immensely valuable if that safe and effective [inaudible] recognized by health authorities as appropriate for clinical use. Thank you for your attention, I'll now invite Dr. Clive Ballard to speak to Studies 019 and 020.

Applicant Presentation – Clive Ballard

DR. BALLARD: Thank you. Good morning. I'm Clive Ballard, an academic, old-age psychiatrist from the UK. I've been researching dementias for most of my career and have led many of the pivotal randomized clinical trials, focusing on pharmacological and non-pharmacological treatments for psychosis and other neuropsychiatric symptoms in people with dementia. I've also led much of the work demonstrating the limited benefit and significant harms of atypical antipsychotics in these individuals.

I know firsthand, from my work with patients, that the related psychosis across dementias can be devastating and debilitating, and I'm passionate about the development of safer and

more effective treatment for this most vulnerable group of patients.

Whilst I treat patients in the United Kingdom, much of the practice is the same, and we experience the same treatment gaps that are evident in the United States. I was the principal investigator of Study 019, chaired the steering committee, and was closely involved in the design of Study 020. The evidence of efficacy for pimavanserin in ADP is primarily derived from those positive studies. Further supportive evidence comes, for efficacy, from Study 045 in patients with dementia-related psychosis and additional post hoc analyses of the Alzheimer's disease psychosis subgroup, supporting consistent benefit of pimavanserin treatment.

I will discuss biological and clinical evidence regarding the close relationship between Alzheimer's disease psychosis and Parkinson's disease psychosis, and data from Studies 019 and 020, providing evidence for the efficacy of pimavanserin in Alzheimer's disease psychosis.

Additionally, I would like to address some pertinent discussion points raised by FDA colleagues, namely the validity and reliability of the neuropsychiatric inventory as the primary outcome measure in Study 019; the meaningfulness, relevant and consistent pattern of the treatment effect; the durability of the effect when controlling for the natural fluctuations in Alzheimer's disease psychosis severity; and the lack of separation on the secondary outcomes for symptoms other than hallucinations or delusions.

Firstly, let me discuss the relationship between Alzheimer's disease psychosis and Parkinson's disease psychosis. Mechanistically, there are substantial similarities between Parkinson's disease psychosis and Alzheimer's disease psychosis. Common brain regions are involved in both conditions. For example, visual hallucinations are associated with hypometabolism or greater atrophy in the occipital cortex and visual association areas of the temporal cortex in both disorders, based on neuroimaging and

post-mortem studies.

The serotonergic system has been highlighted as a key neurochemical underpinning in both disorders, based on neuroimaging, post-mortem, and genetic polymorphism studies. In addition, there is considerable pathological overlap. More than 90 percent of people with Parkinson's disease dementia have significant Alzheimer's pathology, and even in the absence of dementia, almost all people with Parkinson's disease have at least some amyloid plaque pathology.

The clinical picture is also similar in regard to the psychotic symptoms experienced by people with Alzheimer's disease and Parkinson's disease, which are clearly distinct from major psychotic disorders such as schizophrenia. In both conditions, most hallucinations are in the visual modality usually of people, animals, or strangers; the latter often accompanied by the delusional belief that strangers are living in the house.

Although the presentation is extremely similar, visual hallucinations do have a higher

frequency and are less likely to spontaneously recover in people with Parkinson's disease. In both Alzheimer's disease psychosis and Parkinson's disease psychosis, delusions are simple with common themes such as theft, harm, and infidelity.

Much of my work is focused on understanding the natural history of psychosis in people with Alzheimer's disease, which shows a fluctuating pattern of recovery followed by relapse or the emergence of new psychotic symptoms. We found that 68 percent of people recover from their psychotic symptoms by week 12, but the majority of these individuals experience a relapse or the emergence of new psychotic symptoms over the subsequent 6 to 12 months.

Typically across clinical trials in this area, there is approximately a 50 percent short-term improvement in the placebo group, probably driven by a Hawthorne effect. These two effects combined make designing trials for Alzheimer's disease psychosis challenging, and to measure acute treatment response, 6 weeks is the

optimal time point for primary assessment.

Study 019 in patients with Alzheimer's disease psychosis was conducted in 133 nursing care homes with 20 medical subinvestigators in the UK. Brief psychosocial therapy was administered during the screening period to mirror clinical guidelines and ensure they're only patients requiring a pharmacological treatment and to the randomized period of the study.

Patients were randomized 1 to 1 to pimavanserin 34 milligrams once daily or placebo. The primary endpoint was changed from baseline to week 6. In the Neuropsychiatric-Nursing Home Version Psychosis Score, 6 weeks was chosen as the optimal time point to assess pimavanserin's effect on the speed of symptom recovery. Further assessments from weeks 6 through week 12 were included principally to address adverse cognitive and global effects with treatment, an important objective given the well-documented adverse impact of dopaminergic atypical antipsychotics on cognition, mobility, and motor function.

The Neuropsychiatric Inventory was chosen as the primary measure, based on extensive reliability and validation studies and its use in more than 300 clinical studies in Alzheimer's disease. Of particular note, the Neuropsychiatric Inventory has good concurrent validity with other measures of Alzheimer's disease psychosis.

The scale has 12 domains, two of which measure psychosis, hallucinations, and delusions, respectively. Each domain assesses both symptom severity and frequency to produce a total maximum score of 24 for delusions and hallucinations. Whilst the total score is a multiple of frequency and severity, the frequency and severity scores can be examined separately to give a clear picture of the benefit for specific individuals.

Raters were thoroughly trained on the Neuropsychiatric Inventory. To mitigate any potential for expectancy bias, different raters were utilized at consecutive visits for the same patient. Neuropsychiatric Inventory raters were centrally trained by MedAvante. More than 200 NPI

assessments were audio recorded to check and ensure high quality. Regular calibration assessments were performed to confirm adherence to standardized procedures with feedback to raters. The raters also received regular refresher training.

In addition, the informants were all care staff who knew the individual participants well, and all care staff were trained in the Neuropsychiatric Inventory to improve the quality of the informant information. These thorough procedures produced high inter-rater reliability while in excess of 0.9, which is exceptional for a measure of neuropsychiatric symptoms.

Now turning to the results, the study involved an elderly and frail population with a mean age of 86 years and a modest ethnic diversity representative of UK nursing homes. The patients included a representative of a care home population with severe dementia and reflect those patients most in need of treatment. These patients suffered from many comorbidities, and this is in fact one of only four studies that has focused on psychosis

treatment in people with severe dementia.

The study met its primary endpoint, demonstrating a statistically significant greater mean reduction from baseline to week 6 in the Neuropsychiatric Inventory Psychosis Score for pimavanserin compared to placebo. The standardized effect size versus placebo was a Cohen's d of 0.32, which is clinically meaningful and compares favorably with previous studies of atypical antipsychotics, where effect sizes are less than 0.2.

We also evaluated the number of people achieving 30 percent and 50 percent improvement on the Neuropsychiatric Inventory Psychosis Score. The threshold is usually considered to represent meaningful benefit in studies of neuropsychiatric symptoms in people with Alzheimer's disease. The study demonstrated statistically significant benefit at week 6 for participants with Alzheimer's disease psychosis treated with pimavanserin compared to those receiving placebo for both thresholds, with the numbers needed to treat, or

NNTs, of 6 and 7 at 30 percent and 50 percent, respectively.

For context, the 18 percent greater number of people improving by 30 percent relative to placebo compares favorably with an 11 percent advantage from a meta-analysis in studies of atypical antipsychotics, and importantly, benefits compared to placebo are also seen across the full spectrum of improvement.

To further put these data into context and help illustrate the tangible benefits for patients and their caregivers, I've split the NPI data to show the frequency and severity scores for improvement. First in delusions, 25 percent of people treated with pimavanserin improved by 3 or 4 points on frequency, representing a change from multiple times a day to less than once a week, and 30 percent of people treated with pimavanserin improved by 2 or 3 points on severity, representing a change from severe distress to no distress.

For both frequency and severity, these are highly impactful changes that give patients and

caregivers significant relief from the terrible burden of psychosis, moving patients towards fewer weekly symptoms and less severe distress.

Less participants experienced hallucinations at baseline, and they were generally less severe than the delusions. Nevertheless, we see meaningful improvement in both frequency and severity of hallucinations with tangible benefits for patients and caregivers.

Now let's review the subgroup analyses. All subgroups favor pimavanserin and support the primary analysis, including by dementia severity and Alzheimer's disease psychosis that has previously required treatment with atypical antipsychotics. Whilst the benefit observed in the less severe group was modest, there was a particularly favorable response in people with severe psychosis, those patients most in need.

Eighty-nine of participants with severe psychosis at baseline achieved clinically meaningful benefit on pimavanserin compared to 43 percent on placebo. The effect size was

substantially higher, greater than 0.7, a large effect size representing a 4.43-point advantage for the pimavanserin-treated patients compared to placebo, with an NNT of 3. Importantly, these data suggest that those individuals with the most frequent and most distressing symptoms are the individuals who benefit the most from pimavanserin.

Assessments after 6 weeks were all exploratory in nature and focused on safety. As noted earlier, there's a substantial placebo effect up to week 4, and we know from studies focusing on the natural history of psychosis in people with Alzheimer's disease that many patients spontaneously recover over 12 weeks.

It is not, therefore, surprising that whilst the benefits of pimavanserin for the treatment of Alzheimer's psychosis were maintained to week 12, there was also improvement in the placebo-treated group by the week 12 time point, and there was no significant difference between pimavanserin and placebo at that later time.

To further address questions around the

12-week outcomes, we assessed time to improvement for responders who improved by at least 30 percent from baseline. The figure on the left shows patients with symptom improvement at a single time point. The figure on the right shows patients with improvement confirmed for two consecutive time points, indicating sustained improvement.

This analysis reduces the influence of fluctuations in symptoms occurring as part of the natural course of Alzheimer's disease psychosis and highlights the individuals with a meaningful and durable treatment response. This confirms the significant acceleration of treatment response and the extended benefit for pimavanserin over placebo for the full 12 weeks of the study. Similar results were also observed for responders who experienced 50 percent or more symptom relief, with even greater benefit over the full 12 weeks of the study.

Now let's review secondary and exploratory endpoints. The FDA briefing document highlighted the absence of benefit on secondary outcomes, but

it's important to emphasize that none of the secondary outcomes measured hallucinations and delusions. Agitation as a commonly co-occurring neuropsychiatric symptom was measured as a secondary outcome, and no significant benefit was identified overall.

It is interesting to note that in a subsequent publication, we demonstrated a significant benefit in agitation amongst people with a 50 percent improvement in psychosis. I would interpret this as an additional benefit in treating psychosis rather than a primary effect on agitation.

In the context of this study, the Clinical Global Impression Scale was a completely global outcome, encompassing cognition and function, as well as psychosis and other neuropsychiatric symptoms. This was mainly undertaken to evaluate whether there were any detrimental outcomes on overall function, and importantly, no detrimental impact was observed.

Now let's look at cognitive function. As

Dr. Tariot pointed out, a decline in cognitive function is a known side effect of currently used off-label antipsychotics. Pimavanserin treatment had no negative impact on cognitive function. In Study 019, the Mini-Mental Status Examination, or MMSE, was used to measure cognitive function at baseline and throughout treatment. Here are the results, demonstrating no decline in mean MMSE in pimavanserin-treated patients or difference from placebo-treated patients.

We also observed no negative effect on motor function as measured by the Unified Parkinson's Disease Rating Scale or UPDRS Part III. Please note that on this scale, a decrease in score signifies improvement. Scores remain consistent over time, demonstrating no negative impact on motor function, a significant benefit compared to the impact observed with atypical antipsychotics.

To conclude, Study 019 demonstrated positive and meaningful efficacy of pimavanserin in Alzheimer's disease psychosis. The study met its primary endpoint with clinically meaningful

treatment response; accelerated time to symptom improvement; a consistent pattern of benefit across subgroups and sensitivity analyses; and importantly, severe patients experienced the greatest benefits. Additionally, prespecified safety endpoints demonstrated no impact on cognition or motor function.

Now turning to efficacy evidence from Study 020, which led to pimavanserin's FDA approval in patients with Parkinson's disease psychosis, briefly, Study 020 was a randomized, double-blind, placebo-controlled outpatient study in patients with Parkinson's disease psychosis, which as noted is a closely related condition to Alzheimer's disease psychosis, with similar clinical symptoms, similar treatment response, and similar underlying mechanisms for psychosis, with significant pathological overlap.

Patients had a mean age of about 72 years. Brief psychosocial treatment was, again, utilized during this screening period. Participants meeting eligibility criteria at the end of screening were

randomized 1 to 1 to either placebo or pimavanserin 34 milligrams once daily for the duration of the double-blind treatment period.

The primary efficacy endpoint was the mean change in the SAPS-PD score from baseline to week 6. The SAPS-PD is derived from the well-established scale for the assessment of positive symptoms to evaluate hallucinations and delusions. Its assessment approach is similar to the Neuropsychiatric Inventory used in Study 019.

The treatment difference, based on all randomized patients, was 3.06 points with a Cohen's d effect size of 0.50. Of note, patients with cognitive impairment at baseline experienced an even greater pimavanserin treatment effect compared to placebo.

Now let's review Study 020 results in relation to Study 019. The outcomes from Studies 019 and 020 show a consistent treatment effect. In both studies, patients treated with pimavanserin experienced about 2 times greater improvement in symptoms at 6 weeks as compared to

placebo groups. In addition, it is important to note the similarity in placebo response in both studies, reinforcing the discussion earlier about the consistent and substantial placebo response over the first 4 weeks in randomized-controlled trials focusing on Parkinson's disease psychosis and Alzheimer's disease psychosis.

The similarity in treatment benefit is further illustrated in the responder analysis, examining clinically meaningful improvement. Pimavanserin-treated patients experienced more symptom reduction compared to placebo at both 30 and 50 percent improvement cutoffs in both Alzheimer's psychosis and Parkinson's disease psychosis.

To conclude, Studies 019 and 020 provide evidence of efficacy, supporting pimavanserin for the treatment of patients with Alzheimer's disease psychosis. Study 019 was an adequate and well-controlled study that greatly informed our understanding of patients with Alzheimer's disease psychosis. It met its endpoint, demonstrating

statistically significant, but more importantly, clinically meaningful reductions in psychosis symptoms for elderly patients with substantial comorbidities, and was especially effective in those with severe symptoms.

Study 020 provides confirmatory evidence in the closely related condition of Parkinson's disease psychosis. The consistent treatment response between these two studies supports a common clinical presentation of psychosis and a similar response to effective antipsychotic treatment. Pimavanserin would be a substantial advance in the treatment of our patients with Alzheimer's disease psychosis and would address a critical unmet need.

Thank you for your time. I'll now turn the presentation to Dr. Hendrix.

Applicant Presentation – Suzanne Hendrix

DR. HENDRIX: Thank you, and good morning. I'm Suzanne Hendrix, a statistical consultant who has specialized in neurodegeneration for the past 19 years. I will first describe data from

Study 045, and then review exploratory analyses that provide additional supportive evidence of pimavanserin's effect in patients with ADP.

Study 045 evaluated the durability of effect in pimavanserin in patients with dementia-related psychosis or DRP. The study was a double-blind, placebo-controlled, randomized withdrawal design, treating all patients first in a 12-week open-label period, and then randomizing patients to continue treatment or switch to placebo. This mirrors clinical practice and assesses durability of effects.

All patients began on pimavanserin 34 mg once daily with the possibility of an early adjustment to 20 mg. Patients who exhibited a response at both weeks 8 and 12 were then randomized in the double-blind period. The primary efficacy endpoint was time from randomization to relapse of psychosis, based on blinded independent adjudication in the double-blind period.

Aligned with FDA, a prespecified interim efficacy analysis was performed after 40 relapse

events, using an O'Brien-Fleming stopping boundary of a one-sided. alpha 0.0033. All analyses were prespecified for the ITT analysis set in all DRP patients.

This study was conducted in an elderly population, two-thirds of whom had Alzheimer's disease. The SAPS-H+D and MMSE scores reflect moderate dementia and moderate to severe psychosis. The baseline demographic and disease characteristics were similar at randomization and were also balanced between the pimavanserin and placebo groups prior to the double-blind period.

During the open-label period, pimavanserin treatment resulted in substantial improvement in psychotic symptoms, as shown in this figure, with a mean reduction of nearly 20 points on the SAPS-H+D score. Additionally, the improvements observed in the ADP and PDD subgroups were very similar to the overall DRP population. Approximately 60 to 70 percent of patients experienced sustained response and were randomized into the double-blind period. Complete symptom resolution was achieved

in approximately 20 percent of patients overall.

The study met the primary endpoint at the interim efficacy analysis with a 2.8-fold risk reduction and a p-value of 0.002. The hazard ratio was 0.35, showing pimavanserin significantly reduced the risk of relapse of psychosis in the overall DRP population, meeting the prespecified stopping criteria. The independent data monitoring committee recommended stopping the study due to this robustly positive efficacy finding.

Additionally, the study met the key secondary endpoint of time to all-cause discontinuation, a measure of both efficacy and tolerability, demonstrating significantly lower discontinuation with pimavanserin versus placebo.

The study was positive overall in DRP, and we additionally explored the contribution of dementia subgroups although the study wasn't powered to show statistical differences. In patients with ADP, we observed a hazard ratio of 0.62, consistent with a clinically meaningful 40 percent reduction in risk that was not

statistically significant. For patients with PDD, which represented about 18 percent of the overall population, the hazard ratio was 0.05, corresponding to a remarkably high 95 percent reduction in risk.

Based on these results, the FDA questioned the originally planned broad indication for the treatment of DRP. We also wanted to understand why PDD performed better than the other dementia subgroups.

Due to the exploratory nature of these analyses, all p-values are nominal and used for descriptive purposes only. The Kaplan-Meier plot on the left shows the placebo group, which has clear heterogeneity between PDD and the other subgroups, but on the right for pimavanserin, we see homogeneous maintenance of response across dementia subgroups.

These results suggest that the dementia subgroups differ in pattern of response only when pimavanserin is withdrawn, resulting in the larger treatment difference observed for PDD. This faster

relapse rate after treatment withdrawal for patients with PD is likely due to the use of dopaminergic medication such as levodopa, which are known to contribute to the psychosis symptoms. Non-PDD patients taking these medications showed consistent results with PDD.

Finally, the next several slides will focus on support of exploratory results just within the ADP subgroup. In addition to the ADP subgroup, I'll present the ADP 34-mg subgroup, as 34 mg is the dose that was used in the 019 and 020 studies, and is the FDA-approved dose for the treatment of PDP.

In Study 045, all patients who were stabilized on pimavanserin 34 mg prior to randomization were either randomized to stay on pimavanserin 34 mg or switch to the corresponding placebo arm. Nearly all patients were stabilized on pimavanserin 34 mg; in fact, only 7 patients, or 6 percent, received pimavanserin 20 mg.

The full ADP subgroup demonstrated a nearly 40 percent reduction in the hazard of relapse,

corresponding to the Kaplan-Meier curve shown here on the left; and on the right, the ADP 34-mg group is shown with a 53 percent reduction in relapse risk.

An exposure-response analysis was performed to assess the relationship between PK exposure and the risk of relapse, based on DRP and ADP populations. In the ADP subgroup specifically, this analysis gives a hazard ratio of 0.47, corresponding to a 53 percent reduction in risk of relapse at the median AUC.

We agree with the FDA's conclusion in their briefing document that within ADP, higher PK exposures were associated with a higher relapse-free probability. This analysis indicates that the treatment effect in the ADP subgroup is due to a pharmacological effect of pimavanserin, consistent with the original effects seen in the prespecified primary analysis for overall DRP, providing another source of evidence that supports the effectiveness of pimavanserin in ADP patients.

In order to explore different responder

rates, we started by comparing the percentage of patients within each treatment arm who did or did not experience symptom worsening. You can see that 60 percent of pimavanserin patients did not worsen compared to 48 percent on placebo. Among those who did worsen, the opposite relationship is observed on the right, with fewer patients on pimavanserin experiencing any worsening.

When we further break down those who worsened by additional thresholds of worsening, we see that at all levels of worsening on the SAPS-H+D scale, pimavanserin shows less worsening than placebo; and in fact, at a 6, 9, or 12-point threshold, pimavanserin has half as many patients experiencing those higher levels of worsening, consistent with a clinically meaningful effect.

Similarly, we observed this pattern of response with continued pimavanserin treatment versus placebo when assessing the CGI-I, a global clinical assessment of psychosis, with the majority of patients improving or remaining stable; again, avoiding the clinically impactful worsening

observed in the placebo arm.

Exploratory endpoints also show consistent benefit in Study 045 and reflect several perspectives of patient well-being in addition to the primary relapse criterion, which was assessed by blinded raters. The SAPS-H+D is based on a clinician's direct assessment of symptoms and the CGI-I is a clinician's global assessment.

The Zarit Burden Inventory reflects the caregiver's burden, and the Quality-of-Life Scale on the bottom assesses quality of life of the patient. The exploratory variables of SAPS-H+D and CGI-I both achieve statistical significance for the ADP subgroup. The last two exploratory outcomes, Zarit Burden Inventory and Quality-of-Life Scale, also show directionally consistent effects. All of these perspectives show consistent and meaningful effects supporting pimavanserin in ADP.

Realizing that this study wasn't powered to assess dementia subgroups, and knowing the potential for imbalances in subgroups, we conducted a covariate adjusted model to correct for potential

confounding factors known to be clinically important. Here I show the results of that model, as well as several models proposed by my FDA colleague.

It is important to note that regardless of the approach used for covariate adjustment, the resulting point estimates for hazard ratios are consistent, and all fall within a clinically meaningful range of 0.48 to 0.64 for the ADP subgroup overall, and 0.35 to 0.49 for the 34-mg dose, which is our target.

To summarize, the evidence of efficacy is consistent and clinically meaningful. This efficacy has been observed across studies, including Study 019 in the target population of ADP; Study 020 in a closely related condition of PDP; and from Positive Study 045 in DRP, with exploratory analyses in the large ADP subgroup that positively inform our understanding of treatment effect for pimavanserin.

The totality of efficacy data presented by Dr. Ballard and myself support a true and

meaningful benefit of pimavanserin for patients with ADP. Thank you. I'd now like to turn the presentation to Dr. Turner to present the safety data.

Applicant Presentation – Mary Ellen Turner

DR. TURNER: Thank you, Dr. Hendrix.

My name is Mary Ellen Turner, and I'm senior vice president of pharmacovigilance and corporate safety officer at Acadia. While we agree with the FDA there are no safety issues to discuss, I'd like to provide information regarding a favorable tolerability and safety profile of pimavanserin to inform the benefit-risk discussions.

Pimavanserin has a well-characterized and favorable safety profile. Across the clinical development program, more than 3,500 patients have been exposed to pimavanserin. This expanded safety data set includes the largest clinical program in patients with neurodegenerative disease or NDD. Pimavanserin's postmarketing experience spans more than 6 years and 44,000 PDP patients. The safety profile in the Alzheimer's disease population is

favorable and consistent with the known safety profile of pimavanserin.

I will present the key safety and tolerability features that differentiate pimavanserin from the current standard of care. These include favorable mortality trends, as well as no negative impact on cognitive or motor function.

Let's review mortality findings, which included over 1,500 elderly patients from our clinical trial program in NDD, comparing pimavanserin with placebo patients. In the first line, you will see the incident rate ratio of 1.02 for deaths within 30 days of last treatment received.

For deaths within the study intended treatment period plus 30 days, the incident rate ratio is 1.28. For clarity, the difference between these two analyses is 2 patient deaths that occurred more than 30 days after discontinuing therapy, but still within the intended study period. Both show wide confidence intervals due to

small sample size relative to our postmarketing experience.

These mortality rates are lower than the mortality rates in the original PDP safety data set, and as our clinical safety data set increases in size, the mortality point estimate has become more precise and trends towards placebo. Additionally, since pimavanserin's approval in 2016, Acadia has closely monitored the safety profile in the postmarketing setting.

Large observational studies comparing pimavanserin mortality rates with antipsychotics used off-label provide real-world evidence in populations that complement the mortality analysis of pimavanserin from clinical trials.

Here we present two recent large Medicare claims data studies of mortality in patients with Parkinson's disease and in patients with PDP treated with pimavanserin or other antipsychotics. Mosholder and colleagues evaluated all-cause mortality in patients with Parkinson's disease and reported a statistically significant hazard ratio

of 0.78, favoring pimavanserin. A subsequent Acadia-sponsored Medicare safety study by Layton and colleagues demonstrated identical findings with a hazard ratio of 0.78.

As previously noted, in our clinical studies we've observed that pimavanserin has no negative impact on cognitive function. Here I share data from the open-label period of Study 045. The mean change from baseline to week 12 in MMSE score was 1.0. During the double-blind period, there was no decline in mean MMSE in pimavanserin-treated patients.

Here you can see the full picture of the Study 045 completers, starting from open-label baseline to the 26-week double-blind period, again showing stability in the mean MMSE. Additionally, here are the MMSE findings for pimavanserin compared to those for other antipsychotics used in elderly dementia patients, taken from the Schneider meta-analysis that Dr. Tariot presented earlier. Again, we see no negative impact on cognitive function with pimavanserin in contrast to other

antipsychotics.

Additionally, in Study 045, there was no observed worsening in motor function in pimavanserin-treated patients, as measured by the change in Extrapyramidal Symptoms Rating Scale-A or ESRS-A. During the open-label period, the ESRS-A was measured at baseline and at week 12, and showed a trend towards improvement and no worsening of motor function. Again, here the [indiscernible] score signifies improvement.

Shown here is the double-blind period during which the mean change from baseline was small and similar in the two treatment groups at all time points.

In conclusion, pimavanserin has a well-established, consistent, and favorable safety profile across the largest clinical safety data set in patients with NDD, supported by favorable findings from observational studies and our extensive postmarketing experience. Pimavanserin is well tolerated and differentiated from other antipsychotics currently used off-label. Observed

mortality rates are trending favorably. Additionally, pimavanserin has no negative impact on cognitive or motor function.

Thank you. Dr. Stankovic will now provide a benefit-risk assessment.

Applicant Presentation – Serge Stankovic

DR. STANKOVIC: Thank you, Dr. Turner.

I'm Serge Stankovic, president of Acadia. I would like to conclude today's review of pimavanserin data in ADP with a discussion of benefit-risk. As you heard today, ADP is a serious and debilitating condition with severe consequences for patients and their families. It results in significant mental and physical distress; acceleration of cognitive impairment; nursing home placement; and increased mortality and morbidity.

Unfortunately, there are no currently approved treatments for patients with ADP. In the absence of a safe and effective treatment option, the antipsychotics used off label to treat psychotic symptoms associated with dementia expose these frail and elderly patients to great risk, as

they can worsen the underlying condition with marginal to no benefits.

We presented today consistent, robust, and clinically meaningful efficacy across multiple studies, endpoints, and over time. Taken together, the aggregate data set provides evidence of effectiveness in ADP. What constitutes evidence of effectiveness of pimavanserin in ADP is a topic of discussion today.

In 2019, FDA issued draft guidelines relevant to this topic. It states, "One adequate and well-controlled clinical investigation, plus confirmatory evidence in a closely related approved indication, can be sufficient to establish effectiveness."

Consistent with the above guidance, Acadia presented today data from three positive studies in psychosis: Positive Study 019 in the target indication of ADP; confirmatory evidence from Positive Study 020, the closely related approved indication of PDP; and additional supportive evidence from the ADP subgroup from the overall

positive study in DRP, Study 045. The totality of efficacy data presented reliably meets the standards for evidence of effectiveness in ADP. Particularly important, this efficacy was observed in the context of a favorable safety profile.

In conclusion, pimavanserin provides clinical efficacy benefit to patients with ADP, and would allow them to manage their psychosis while not exacerbating the underlying condition or introducing new safety risks such as cognitive or motor impairment. The totality of data presented today supports a positive benefit-risk profile of pimavanserin for the treatment of hallucinations and delusions associated with ADP. Perhaps most important, this is in the context of a disease where there are no approved treatments, and the current standard of care has marginal benefit with considerable risks.

Thank you. I will now invite Mr. DeKarske to return to moderate the question and answer session.

DR. NARENDRAN: This is Raj Narendran. It

seems like we're ahead of schedule.

I do want to give an opportunity for Dr. Paul Stander, who joined us later, to introduce himself.

(No response.)

DR. NARENDRAN: Dr. Paul Stander, if you want to introduce yourself?

DR. STANDER: Yes. Thank you. This is Dr. Paul Stander. I am the associate chief of staff for Geriatrics and Extended Care at the Phoenix VA, and I am a clinical professor at the University of Arizona, College of Medicine, Phoenix. I'm sorry. I had a few issues early this morning, but I was able to hear the majority of the presentations. Thank you.

Clarifying Questions to Applicant

DR. NARENDRAN: Thank you, Dr. Stander.

We will now take clarifying questions for Acadia Pharmaceuticals. Please use the raise-hand icon to indicate that you have a question, and remember to clear the icon after you have asked your question. When acknowledged, please remember

to state your name for the record before you speak and direct your question to a specific presenter, if you can. If you wish for a specific slide to be displayed, please let us know the slide number, if possible.

Finally, it would be helpful to acknowledge the end of your question with a thank you or say you have a follow-up question to ask, and that way we can then move to the next panel member.

The first question we have is from Dr. Fiedorowicz.

DR. FIEDOROWICZ: Yes. Thank you. This is Jess Fiedorowicz from the University of Ottawa. I have a clarifying question.

A lot of the slides and results for Study 019 hinge on this primary outcome, where the time frame is stated to be 6 weeks. My clarifying question is that in both the Lancet paper and the clinicaltrials.gov registration, study completion is listed as October 27th. All registrations prior to that date show 12 weeks as the time frame after the primary efficacy outcome, and the only

registration that shows 6 weeks occurs on July 14th of 2017, as you can tell, several months well after the close of this study.

I was wondering if the applicant can clarify that. Thank you.

MR. DeKARSKE: Thank you for the question. I'm happy to clarify.

The original Study 019 protocol that was submitted to the FDA and to the IND had a 6-week primary endpoint, so the day 43 endpoint that was discussed in the core presentation. That endpoint remained throughout the conduct of the study, up to unblinding.

I'll note your reference to the clinicaltrials.gov website. There was additional clarification subsequent to the trial's start. It was initially indicated as a 12-week treatment period, which was indeed true, but there was additional clarification subsequently to be clear that the primary endpoint was at 6 weeks. But I just want to emphasize that, again, the 6-week primary endpoint was part of the original protocol

upon execution of the study.

DR. NARENDRAN: Our next question is from Ms. Witczak.

MS. WITCZAK: Thanks for your presentation; Woodymatters, for the record. I know the original application to the FDA was for dementia-related psychosis, and then it switched over to Alzheimer's disease psychosis.

My question is, were brain scans or other scans used to objectively diagnose that it was Alzheimer and/or was it able to differentiate from other causes of dementia? So that's my question.

MR. DeKARSKE: Thank you for the question.

The diagnoses were clinical diagnoses for Study 045. I'd like to ask Dr. Serge Stankovic to please speak to the inclusion criteria, then I'd like to ask Dr. Pierre Tariot for follow-up after Dr. Stankovic.

Dr. Stankovic?

DR. STANKOVIC: Serge Stankovic, Arcadia. Study 045, our dementia-related psychosis study, used clinical diagnosis for different dementia

subtypes. The study protocol asked the investigator to indicate which dementia subtype is primary dementia subtype from the clinical perspective and clinical diagnosis, and obviously they used internationally accepted criteria for diagnosis. But there were not any biomarkers used in the study for the diagnosis of subtypes.

The reasons for that were, number one, there is a significant overlap in the underlying neuropathology in the patients of the advanced dementia with psychotic symptoms; and second, the nature of the study was that we were approaching all-comer dementia-related psychosis regardless of the underlying subtype. So from that perspective, a biomarker diagnosis wasn't as important as it would be in the disease-modifying treatment or the study of the specific subtypes of dementia.

Thank you. I'll turn it over to Dr. Tariot.

DR. TARIOT: Thank you. Pierre Tariot here, consultant. Thank you for the terrific question.

Just to build a little bit on what Dr. Stankovic just said, the participants in

Study 045 that you asked about were, as you heard, aged, frail, and they had advanced dementia and psychosis. So these would not be appropriate candidates for lumbar puncture or amyloid PET scanning; lumbar puncture to collect the CSF to look for elevated amyloid and/or tau.

I agree with what Dr. Stankovic just said. We're very interested in the use of imaging and fluid biomarkers to improve diagnostic accuracy for the presence of Alzheimer's pathology, but in milder forms and milder severity of Alzheimer's disease in younger patients.

This might be a follow-up question of yours. No, there are not plasma samples retained from the study, so we don't have the opportunity to look at those retrospectively. And again, just to repeat this point that I think is quite important; persons with advanced dementia have a high likelihood of having multiple pathologies, so even if we had had a way to establish the presence of elevated brain amyloid, it wouldn't rule out other pathologies.

I guess the last point I'd like to make is

that the study was designed as a kind of pragmatic clinical trial to inform clinical practice, and at least then -- and it's changing, but at least then, and even now I would submit, the currently available research in biomarkers are not yet widely used in clinical practice. Thank you.

DR. NARENDRAN: Our next question is from Dr. Apostolova.

DR. APOSTOLOVA: Yes. Can you hear me?

DR. NARENDRAN: Yes, we can hear you.

DR. APOSTOLOVA: First off, I'm glad I'm actually following Pierre in my commentary here because, to me, it looks like there is effect observed in both PDD and AD psychosis. However, it's weaker in AD psychosis, and I wonder to what extent does the presence of alpha-synucleinopathy in amygdala limbic parts actually contributes to that.

Alpha-synuclein is a known copathology in Alzheimer's, present in 40 percent possibly, so it might be that the strong responders are those who have Lewy body pathology in at least limbic areas,

but how do we know that? There is the already quick [ph] assay, but again, it's CSF, and as Pierre pointed out, that is not attainable in advanced subjects.

My question, though, is about the durability of effect, and it's probably directed to Suzanne Hendrix. Slides 29 and 34 from the presentation do show that, over time, regardless of continuous treatment, placebo tends to sort of merge towards the treated group, and the difference is no longer significant.

How can that be explained scientifically and statistically? Could it have something to do also with measurement subjectivity, as we don't have biomarkers, which are objective measures of treatment response, as opposed to subjective measures like NPI? And I'm wondering both what Suzanne and maybe Pierre think about that. Thank you.

MR. DeKARSKE: Thank you for the question. I just want to clarify, you're referring to Study 019; is that correct?

DR. APOSTOLOVA: So slide 29, Study 019, and then slide 34, both --

MR. DeKARSKE: Thank you.

DR. APOSTOLOVA: -- yes.

MR. DeKARSKE: Very good.

I'd like to ask Dr. Clive Ballard to comment a little bit further on Study 019, particularly in the durability of effect point. But perhaps, Dr. Ballard, you could also circle back on the question about the comment in overlapping neurobiology and neuropathology between ADP and PDP.

Before I ask Dr. Ballard to comment, I just do want to remind that Study 019 had a 6-week primary efficacy endpoint, and that the endpoints beyond 6 weeks were exploratory in nature, mostly from the perspective, as you heard Dr. Ballard comment, of a safety standpoint with respect to looking for any potential negative impact on cognition.

In Study 045, the randomized withdrawal study, which is a very conventional design to

establish maintenance of efficacy, was intended to demonstrate that, following the acute response that was shown in Study 019 and Study 020.

Dr. Ballard, can you please comment further?

DR. BALLARD: Thank you. Clive Ballard.

Firstly, looking at the main outcome slide at week 6, as you say, that was the primary endpoint and the clinically meaningful benefit, as well as statistically significant benefit as indicated by a benefit at 30 percent level of improvement and 50 percent level of improvement. The study was really designed to focus on acute benefit, and 6 weeks was the selected period, very deliberately, for that outcome

When we're trying to understand longer-term effects, we have to do that in the context of the natural history of the disorder. We conducted a study where we followed people up every month to look at the ongoing course of the symptoms. As I mentioned in the core presentation, over two-thirds of patients had resolution of those symptoms by 12 weeks, but the underlying pattern is a lot of

fluctuation, and a lot bouncing around of these symptoms, a bit of improvement; a bit of worsening; recovery; relapse again.

So although there's an overall enduring pattern of these symptoms, it's very much an improved, get worse, recover, relapse type pattern. And certainly over 12 weeks, in the relatively short term, there's a lot of spontaneous recovery as part of this fluctuating pattern of symptoms.

I mean, whether that's due to the way that we measure symptoms it's difficult to know. What I can say is the Neuropsychiatric Inventory is a well-validated scale, and within this particular study, we went to great lengths to both train the raters very thoroughly, but also to train the informants, the caregivers giving the information, in the scale to really try and make it as tight as possible. And I think the fact that there was a very high inter-rater reliability greater than 0.9 shows that we were fairly successful in doing that.

In this type of population of people with severe dementia psychosis and a lot of comorbidity,

biomarkers are kind of a challenging thing to do, and I don't think anyone's yet demonstrated the utility of biomarkers as an outcome for psychosis in people with dementia. So I think although I'm sure that will be evolving space, I think where we're at, at the moment, is that we have to rely on robust clinical judgment.

What we did do -- and perhaps I'll ask Dr. Hendrix to comment a little bit further on the analysis -- is to try and understand the pattern of ongoing response beyond 6 weeks by trying to take out that impact of that fluctuating, improving, relapsing kind of course. And the way that we did that is by requiring people to have two consecutive improvements so that they had to be improved at two consecutive assessment points in a time to response analysis.

When we do that, you can see there in the figure on the right, that that takes a lot of the noise out, it takes a lot of this fluctuation and severity out, and what you see then is you have an improved early response in pimavanserin, but also

that response is sustained over a longer period of the study through to the 12 weeks.

I know you asked Dr. Hendrix to comment further, so I'm not sure, Dr. Hendrix, whether you'd just like to comment on the statistical approach that you took.

DR. HENDRIX: Yes. Thank you, Dr. Ballard. Suzanne Hendrix, statistical consultant.

If we could just pull up for a minute the slide that shows those plots coming back together at the end, and actually let's first do CO-29; that was the original question.

So this plot, because it's actually a cumulative distribution plot, the far right of the plot isn't time and coming back together after time, but it's actually the number of people who have achieved 100 percent improvement on their NPI-NH score on the psychosis component. Over to the right, there aren't as many people; in fact, there are equivalent numbers in the placebo and pimavanserin groups who've achieved a hundred percent response, but we see really strong

separation at the clinically meaningful 30 and 50 percent effect time points.

Now, the analysis that Dr. Ballard was referring to, just to point out again that when we look for consistent benefit, the active arm has substantial benefit; pimavanserin has substantial benefit over placebo. And here, when you're looking at the pattern over time, pimavanserin maintains benefit all the way out to 12 weeks. It's the placebo group that comes back down, and that's due to the symptom relapsing and coming back out. Then the slide that he showed that shows the consistent confirmed effect across two visits, then we continue to see that separation between the active arms.

So all this speaks to two things; number one, a consistent benefit of pimavanserin out to 12 weeks that is then confirmed in the 045 data and a clinically meaningful effect that, again, is also confirmed in the 045 data.

MR. DeKARSKE: Thank you.

May I have slide CO-57 quickly, please?

Just circling back around on the maintenance of efficacy point, as I mentioned, following acute response demonstration in both Study 019 and Study 020, we specifically endeavored to look at maintenance of efficacy in Study 045.

As you heard Dr. Hendrix speak to earlier, we saw a very statistically significant result in the overall DRP patient population. But in the context of doing further exploration of a positive study, looking at the ADP subgroup, both all doses of ADP, as well as ADP 34 milligrams, we saw a clinically meaningful reduction in the risk of relapse in that large ADP subgroup, around 40 to 50 percent, which for these types of trials is very well recognized as a clinically meaningful reduction in relapse.

If I may briefly, I'd like to ask Dr. Leslie Citrome just to speak on the clinical meaningfulness of the hazard ratio in this patient population.

Dr. Citrome?

DR. CITROME: Leslie Citrome. I'm a

psychiatrist, and I work with patients, and I do research. One of the things I do is look at the clinical meaningfulness of clinical trial results in systematic reviews, and across the field of psychiatry, whether we're looking at schizophrenia or bipolar disorder, or major depressive disorder, and we look at the maintenance of effect studies, a hazard ratio will describe the likelihood of relapse or recurrence, or a given period of time in people who have been stabilized on a medicine of interest, and then randomize to either continue that medicine of interest or go on to placebo.

This hazard ratio over the course of the period of the study has ordinarily been around about 0.5, hovering around there. We would say that people who are maintained on the medicine that got them well were half as likely to experience a recurrence or relapse than compared to those who are randomized to go on to placebo. So what we see, actually, is entirely consistent with clinical trials within psychiatry, so I'm not at all surprised by these results. Thank you.

DR. NARENDRAN: Our next question is from Dr. Thambisetty.

DR. THAMBISETTY: Thank you, Dr. Narendran. This is Madhav Thambisetty from the NIH. I have a comment and accompanying question. My comment is about slides 28, and even slide 43 from the efficacy presentation.

I find it somewhat troubling that these graphs are curtailed at the 6-week time point when you have a full data set that extends through to 12 weeks. And I think it's potentially misleading to show graphs curtailed at 6 weeks when you have a full data set at 12 weeks. It's potentially misleading because this graph seems to indicate that there's a divergence in the placebo and treatment groups, which may be continued beyond the 6 weeks, which clearly is not the case. So I would really like to see these graphs show the full data set rather than just break them at 6 weeks, which brings me to the accompanying question.

This is a follow-up question from what Dr. Fiedorowicz asked first off, and I'm not sure I

understood the explanation provided in response to that question. So I'll state this question again because I really think it's very important.

The public record on clinicaltrials.gov has a history of changes made to the protocol from the study start date in 2013, and it looks as if all versions of the protocol are until July 2017 on clinicaltrials.gov, which consists of information provided by the sponsor clearly prespecifies a primary endpoint outcome at 12 weeks.

It doesn't include July 14, 2017, that the record indicates that the primary outcome was changed from 12 weeks to 6 weeks, which is nearly 10 months since the last patient was randomized. And then on September 28, 2017, again, clinicaltrials.gov indicates exactly one year after the last patient was randomized, the primary endpoint is again changed from 6 weeks to 43 days.

It's not entirely clear to me why a primary outcome endpoint would be changed 10 months to a year after the last patient was randomized. The rationale is not clear to me, and I really don't

know why this was done and what the rationale was. Thank you.

MR. DeKARSKE: Thank you for the question. I'll address your further follow-up on the status of the protocol and the primary endpoint, and I'd like Dr. Clive Ballard to speak to your initial question about the 6 week endpoint relative to the 12-week treatment period.

Could I have slide CO-57, please? I'm sorry; CO-34.

As I mentioned earlier in my previous response, although the trial was a 12-week duration, which was indeed the case, the initial posting for clinicaltrials.gov simply referred to that 12-week period. We subsequently clarified on the clinicaltrials.gov website that the primary was actually at 6, although, again, there was a 12-week treatment period.

Now importantly, in terms of the actual protocol, in its submission to the IND and at the time of its initiation, it had a 6-week trial endpoint. That did not change during the conduct

of the study, nor did it change prior to stopping of the study and unblinding of the data.

Dr. Ballard, could you speak a little bit further to the core slide, CO-34, which shows both the 6-week and the 12-week exploratory efficacy?

DR. BALLARD: Clive Ballard. Certainly.

Firstly, just to confirm about the 6-week primary outcome, as the principal investigator for the study, I was responsible for all of the submission of the protocols to the ethics committee for approval, and I can absolutely confirm, and we can provide the protocols, that the primary outcome was always 6 weeks throughout all of those protocols. So that's definitely not changed it at any point during the process.

To come back to your question about 6 weeks and 12 weeks, I clearly did show this slide showing the full 12-week outcome during the core presentation, so there was no attempt to conceal anything. We initially presented it up to 6 weeks because that's the primary outcome point. The objective of this study was to focus on acute

improvement at 6 weeks with time out to 12 weeks largely to look at safety outcomes because of potential concerns with other atypical antipsychotics in terms of impact on cognition and function.

So I don't think there was any attempt to conceal anything. I presented the data. This placebo pattern that you see over 4 weeks, and then starting to improve at about week 6, this is very consistent across trials of atypical antipsychotics in the literature, which is why we very deliberately chose 6 weeks as the optimal time point to look at the acute response, and that was the intention.

As you can see from the ongoing period, past 6 weeks, as we've already discussed, clearly there's a lot of placebo response over between week 6 and 12. I think that's explained, as I mentioned, by the natural course of the condition, where we know that two-thirds of people in natural follow-up studies are going to have improvement by that 12-week period. So really, the aim of this

study was to look at the 6-week acute response. The aim of the 045 study, given that the nature of this condition is a relaxing, recurring condition, was to look at the sustained benefit and the prevention of relapse in those individuals.

But as I mentioned in the previous response -- if we could just have the slide showing the time-to-response analysis -- one of the things that we did to just try and confirm whether this impact on the loss of response was due to the fluctuation as part of the natural course of the condition, we did do this further analysis, looking at people who'd had sustained benefits at, at least, two time points.

When we did that, and we took the noise out of the situation, we removed the noise from people having brief responses, and then relapses again. When we did that, there was a much clearer pattern of response of pimavanserin in terms of sustained response across the 12 weeks.

DR. NARENDRAN: The next question is from Dr. Cudkowicz.

DR. CUDKOWICZ: Thank you.

I had a question about slide 58, if you might explain a little bit more this exposure-response. I was trying to figure out if they were trying to make the point that you needed higher levels in the Alzheimer's, as that might explain some of the differences between the patients with Alzheimer's versus Parkinson's, and if in fact were there different levels in people with Alzheimer's maybe because of their medications.

MR. DeKARSKE: Thanks for the question. The principal utility for the exposure-response analysis from Study 045 was to reassure on a real pharmacologic treatment effect. So as you heard in the core presentation, what you see in the overall DRP patient population, as well as the ADP subgroup, that the risk of relapse goes down with increasing concentrations of pimavanserin, as also indicated by FDA in their briefing material.

The actual concentration of pimavanserin that you see on the chart in the ADP and the DRP

are quite close. In fact, the steady-state concentration that you would anticipate with the 34-milligram once daily dose is very well reflected as part of this exposure-response analysis. The profile, the pharmacokinetic profile, is what we would expect of the two populations, are consistent.

DR. CUDKOWICZ: Thank you. I just have one other question on another topic, which goes back to this question of duration of treatment. Do you anticipate treating participants or people for 6 weeks, or 12 weeks, or how would this be in clinical practice in the Alzheimer's population?

MR. DeKARSKE: Thank you for the question. The three clinical study data sets, that we have that are supportive of evidence of efficacy in ADP includes both Study 019 and 020, are demonstrating acute response in both ADP and PDP patients.

As I mentioned earlier, Study 045, which is typically done in the psychiatry space, after demonstrating acute response was intended to establish maintenance of efficacy to support

long-term treatment following acute response, positive acute response. So those are intended to support therapy beyond the acute period.

I'll just add its important context with respect to the safety profile of pimavanserin, where we focused on a couple of key safety aspects, that in this class you're particularly concerned about in terms of negative impact on cognition and motor function, we did not observe that, and we were specifically looking in Study 019 and 045 to make sure, with long-term treatment, there weren't any negative impacts.

I'd like Dr. Clive Ballard to provide a bit more clinical perspective on duration of treatment and appropriateness.

DR. BALLARD: Thank you.

I think, obviously, the 6-week effect is really important. These are really distressing symptoms. When they're present, they're very unpleasant for individuals experiencing them and very challenging for everybody, so achieving that benefit over that 6-week period is very, very

important. But I think, potentially, longer term treatment also can be beneficial, and I don't think that's a blanket approach. It's very much based on the needs of individual patients and the pattern and severity of symptoms in individual patients.

But I think one of the challenges we have with currently available atypical antipsychotics is, because of the toxicity issues, longer term treatment for prophylaxis isn't really an option, whereas I think one of the things the relapse prevention data and good tolerability suggest is that that is a potential option.

So whilst that wouldn't be the optimal for every individual, for individuals who do have more severe symptoms, who have higher rates of relapse, I think that that option has been able to provide longer term treatment to reduce relapse safely and to maintain that benefit, and would be a very useful addition to the pharmacological armamentarium for those individuals.

DR. CUDKOWICZ: Thank you.

DR. NARENDRAN: The next question is from

Dr. Walter Dunn.

DR. W. DUNN: Hi. This is Walter Dunn from UCLA. One of the key questions for me for this entire presentation is this notion that -- or this idea that ADP and PDP are closely related conditions. At least from the 045 results, there's some strong indication that there's a differential response, especially when these patients are randomized to placebo; that clearly there is a much higher relapse rate in the Parkinson's patients.

Although you didn't emphasize this in your presentation, in the briefing documents that Acadia provided, the explanation was that this high relapse rate was due to the presence of dopaminergic agents. Unfortunately, the majority of the PDP patients are on those agents, so it's difficult to disentangle between if it's an illness or the presence of those agents.

So I was wondering, do you have data in the open-label period for the patients who did not meet sustained response, and thus did not proceed to the double-blind phase? For those patients who failed

to meet sustained response, do you have any data as far as the distribution of those on dopamine agents versus not?

MR. DeKARSKE: Yes. Thank you. Thank you for the question. Just in following up to your point about our belief that the dopaminergic concomitant therapies were the result of the particularly robust response we saw in the PDD subgroup in the 045 study, I just want to remind that in Study 020, these were PDP patients mostly on dopaminergic medications, and we were looking at improvement in symptoms out to 6 weeks. Study 019, on the other hand, was ADP patients without dopaminergic therapies.

What we saw in those two studies, in those two different patient populations with respect to use of dopaminergic drugs, is a very consistent response. I'm showing slide CO-43 from the main presentation.

As we look at Study 045, and getting to your question in the open-label period, it was reassuring to us that when we looked at the

response rate within the first 12 weeks in the open-label period, we saw a very consistent stabilization between the various dementia subgroups. That includes both PDP and ADP, including what we thought was a very robust complete response at the end of the 12-week period of about 20 percent between the two patient populations.

We don't have on hand right now the distribution within the open-label period, the use of concomitant dopaminergic therapies specifically within the subgroups, but we're happy to provide that after the break.

DR. W. DUNN: Thank you.

MR. DeKARSKE: Yes. But I will say, just following up, in the double-blind period, for those patients that continued from the open-label period into the double-blind period, what we saw was that the patients that continued on pimavanserin, the treatment effect was homogeneous across the subgroups. That includes PDD. It was the placebo group where we saw that there was a very early

relapse, which is what we would expect, based on our belief that the dopaminergic therapies may be exacerbating the underlying psychosis symptoms in the absence of effective antipsychotic treatment. And you can see that clearly here on the core slide CO-54.

DR. W. DUNN: Thank you.

DR. NARENDRAN: Our next question is from Dr. Dean Follmann.

DR. FOLLMANN: Yes. Thank you. I have two questions. I think they're both addressed to Dr. Hendrix.

The first one, in Study 019, you showed a large benefit in people with severe psychosis, with an effect estimate of 0.73 and a p-value of 0.01. And I was wondering if you had looked at the benefit in 045 in those with severe psychosis to try and replicate those.

MR. DeKARSKE: Suzanne Hendrix to come to the mic and speak to your question. Thank you.

DR. HENDRIX: Suzanne Hendrix, statistical consultant. We did look at that, and we found that

those patients who had more room for improvement, which are the ones with more severe symptoms, tended to see more improvement. And in the relapse specifically, we saw that people who were more severe and had treatment removed dropped off more rapidly than those who were less severe. So that same type of pattern of seeing a better effect, where there's more room for an effect, held throughout the 045 data as well.

DR. FOLLMANN: Thank you. I have one more question. If you could bring up slide CO-58 again, this has to do with the effect of drug exposure and the risk of relapse.

Drug levels aren't randomized within the drug group, and it could be that drug levels varied where people who don't comply, or are sicker, or worse outcomes, tend to have lower drug levels. Did you look at the relationship between drug level and baseline characteristics, or compliance, to try and tease at this, to get at this particular issue that we aren't randomizing to drug levels here?

MR. DeKARSKE: Just to point out, the

dropout rate in the open-label period was quite low, in fact; so those patients that were going from pimavanserin in the open-label period into the double-blind period, there were a majority of subjects that were doing so.

I'd like to ask Dr. Suzanne Hendrix to comment, please.

DR. HENDRIX: Yes, it's a very good question because we don't have randomization of those different AUCs. What we did do was we looked at several different covariate analyses, and those covariate analyses tended to make this effect stronger, rather than weaker. Very few of those covariates were actually statistically -- in fact, none of the covariates were statistically significant, and the overall results after adjusting for them were somewhat stronger statistically.

DR. FOLLMANN: Thank you.

DR. NARENDRAN: Our next question is Dr. Apostolova. Do you have another question?

DR. APOSTOLOVA: Yes, I do have another

question. These are super distressful behaviors -- psychosis, hallucinations, delusions -- and they have an incredible impact on caregivers. Was there caregiver distress data collected in these studies? I'm curious what it showed, even though it wasn't presented, if there is any idea. Thanks.

MR. DeKARSKE: Yes. Thanks for the question. There was caregiver burden data that was collected in Study 045, as well as Study 020. I'll just ask Dr. Suzanne Hendrix to speak first to the data in the Zarit Burden interview in Study 045, and what we found.

DR. HENDRIX: Suzanne Hendrix, statistical consultant. On this slide, we're showing the secondary endpoints from the 045 study within the Alzheimer's disease psychosis subgroup specifically, and the SAPS-H+D and the CGI-I were both clinician scales, but the Zarit Burden Inventory, ZBI, shown on the third line here, is a caregiver burden assessment. We did not achieve nominal significance on this test, but we did have

a 1.25 point benefit in favor of pimavanserin, reflecting a clinically meaningful effect for caregivers having less burden.

MR. DeKARSKE: And just following up, in Study 020, this is the study in patients with PDP. The Zarit caregiver burden was also assessed as an exploratory basis, but there was a nominally significant improvement that was seen in the level of burden in those patients.

DR. NARENDRAN: Dr. Walter Dunn, do you have another question? Please go ahead.

DR. W. DUNN: I do. Thank you. Dr. Walter Dunn, UCLA, and another question about Study 045 and the open-label data, if you have it. This speaks to the durability issue again.

Do you have any data on the percentage of patients that, again, did not meet sustained response and did not proceed to double-blind? What proportion would have never met criteria at any of the time points for 8 or 12 weeks versus what proportion of patients potentially at that 4-week time point would have met criteria, but then

symptoms worsened at 8 and 12, and therefore entered the double-blind phase? My understanding is that there was no 6-week study point, so I'm using the 4-week as the proxy for a 6-week time point.

Was I clear in my question?

MR. DeKARSKE: Yes. Thank you. I'm just pulling up slide CO-50 of the open-label period.

To answer the first part of your question, the rate of sustained response or stabilization in the open-label period in the overall group was about 62 percent. This was consistent across the subgroups. And I think as these randomized withdrawal trials go, that's a pretty high stabilization rate. Usually you would see around 40 or 50 percent.

To answer the second part of your question, I'm going to ask Dr. Suzanne Hendrix to please come to the microphone.

DR. HENDRIX: Suzanne Hendrix, statistical consultant. Could you please clarify the second part of your question again?

DR. W. DUNN: I was just wondering what proportion of patients that did not enter the double-blind phase would have met -- did meet entry criteria or would have met entry criteria at 4 weeks, but then relapsed at, we know, weeks 8 or 12, and therefore did not enter the double blind versus what proportion of patients just never improved enough at any time point to enter double blind.

DR. HENDRIX: So the question you're asking is out of that approximately 40 percent who did not meet the enrollment criteria for the double-blind phase, what percentage of those did meet criteria at some of those earlier time points?

DR. W. DUNN: Correct. Correct.

DR. HENDRIX: Okay. Hold on just a minute. We have a slide for that. It's buried a little bit deep. We'll find it, though; one minute.

We'll go ahead and bring that up after the break rather than waiting now.

DR. W. DUNN: Okay. Alright. Thank you.

DR. NARENDRAN: The next question is from

Ms. Witczak.

MS. WITCZAK: Yes. Kim Witczak, Woodymatters. I would like to know the philosophy or the rationale behind using a largely primarily white audience in this clinical trial. Obviously, I know that was in the UK, but in the U.S., the high prevalence is in the African American community and Hispanic. So I'm just curious how that may or may not -- and it might also be a question for the FDA as well; the rationale behind that audience makeup. Thank you.

MR. DeKARSKE: Yes. Thanks for the question. We recognize this is an issue for our industry, including for us at Acadia. That said, pimavanserin's PK profile data, the clinical study, and our postmarketing experience we feel is generalizable to other races and ethnicities. In fact, as our development has ensued with pimavanserin, we've improved on a representation of race and ethnicity.

We had a postmarketing study commitment upon the original approval to increase the safety data

in frail and elderly patients, including Alzheimer's disease patients, which, as you heard Dr. Turner speak to earlier, we've expanded significantly. As you can see, we've got reasonably good representation within the Hispanic and Latino ethnicity; we're improving with black or African-American. But importantly, from a pharmacokinetic perspective, we have done work to identify that pimavanserin's plasma profile is not impacted by race or ethnicity.

That all said, in the go forward, we are doing phase 4 studies, and we're working with specialty sites and minority communities to improve diversity, as we know it's important to inform on that point for our label and for prescribers. But just to land, we do believe it's generalizable with the data we have in hand, both from a PK perspective, from a clinical study perspective, as well as postmarketing experience that doesn't indicate a differential impact with race or ethnicity.

DR. NARENDRAN: We have another question

from Dr. Thambisetty.

DR. THAMBISETTY: Thank you, Dr. Narendran. Madhav Thambisetty, NIH. This is a question directed to the director of the Division of Psychiatry from the FDA on her presentation with slide 8. Maybe this is a question that might be best to be asked after the agency makes their presentation, but I just thought I'd like to bring this up now.

DR. NARENDRAN: I'm sorry to interrupt, but I think it might be better to just ask that during the agency as their own time --

DR. THAMBISETTY: Okay.

DR. NARENDRAN: -- so that way, the sponsor lose their time to answer their questions, if that's ok.

DR. THAMBISETTY: Okay. Yes.

Can I have a quick follow-up question --

DR. NARENDRAN: Sure.

DR. THAMBISETTY: -- about the design of Study 045?

DR. NARENDRAN: Please go ahead.

DR. THAMBISETTY: Yes. This is addressed to the sponsor, and I guess anybody can answer it.

It's very difficult to find a randomized withdrawal trial in psychiatry that hasn't been effective. I think these designs lend themselves to invariably favoring drugs over placebo because there's a tautology involved in the design of the study itself. You're selecting out treatment responders in the open-label phase. You're excluding everybody in the placebo group who might have responded. You're excluding people with adverse events. And then in the double-blind phase, you're again measuring the same thing that you measured in the open-label phase, so in fact, treatment response has been measured twice.

So this study design invariably results in outcomes that unequitably favor drug over placebo. And again, I would maintain that while these designs might be suitable to look at durability of the response, they do not provide a lot of useful information in determining efficacy. There is also concern that during the open-label phase, effects

of drug withdrawal are almost invariably confounded with the relapse itself.

So for these reasons I think randomized withdrawal trials designed especially in psychiatry where you do not have independent outcomes being measured during the true phase of the study, I think they are far from desirable. And again, this is a question that would be suitable both towards the sponsor, as well as to the FDA itself. Thank you.

MR. DeKARSKE: Thank you for the question. Just for context, generally, these randomized withdrawal or maintenance studies are done following demonstration of acute response, which in our case, acute response was demonstrated in Studies 019 and 020.

So that said, in the open-label period of Study 045, as I mentioned earlier, the response rate was quite high. It was over 60 percent in these patients, so there was good evidence that there was a high response rate.

That said, I'd like Dr. Serge Stankovic to

comment further on the randomized withdrawal design and the level of evidence for the overall package for the effectiveness in ADP patients.

Dr. Stankovic?

DR. STANKOVIC: Thank you. Serge Stankovic, Acadia. Thank you, Dr. Thambisetty, for that question. It's a very important question.

The rationale for using the randomized withdrawal design for Study 045 was based on essentially the evolution of our development program. We had already demonstrated acute efficacy in two models of dementia in PDP and in ADP, in the acute setting.

Second, as you pointed out, and others, Study 019 left open a question of whether there is durability of effect because we did not see separation in a week. So the best way to test the maintenance of effect of drug is one of the maintenance of efficacy designs, and that's certainly a randomized withdrawal trial, and that is what we proposed. And the FDA agreed at the end of the phase 2 meeting that it's a reasonable

design as a pivotal trial for the dementia-related psychosis program as a next step in our development program.

In addition, a randomized withdrawal design has obviously some advantages that are important for the patient population that we studied. It minimizes exposure to an effective treatment, and this severe and serious medical condition allows enrollment of patients and their caregivers in the trial because they initially do not have concerns about actually exposing their family member to ineffective treatment, and there are obviously [indiscernible] criteria following randomization.

So it's a design where families are more willing to participate in the trial, and really mimics fairly well the standard of practice in treating these patients. So for all these reasons, this design was chosen and agreed upon for moving into the development of the DRP. Thank you.

DR. NARENDRAN: Thank you. This is Raj Narendran, and I have my own question.

I was just curious. It seems like looking

at Dr. Tariot's presentation, the objective of having an antipsychotic or a medication to treat psychosis in Alzheimer's dementia is to keep patients out of a nursing home, and prevent deterioration, and improve their functioning.

Why was it that 019 was done in a nursing home where patients are extremely cognitively compromised with a very low mini-mental status, as opposed to 045 seems to be more like your target population you want to go for?

MR. DeKARSKE: Thanks for the question. I'll just point out quickly, before I turn it over to Dr. Ballard to answer your question on 019 in the nursing home population, Study 020 was also an outpatient study. So across the spectrum of patients that are in a nursing home or an outpatient basis, we have representation of efficacy and safety data.

But specific to the advanced age and disease for Study 019, Dr. Ballard, can you please explain the design?

DR. BALLARD: Thank you. Clive Ballard.

I think both are really important. I mean, obviously, for people living at home with family members or living on their own, trying to help those individuals retain independence and reduce the chances of individuals moving into institutional care is really important, but I think we shouldn't also forget the high levels of distress and vulnerability of people already in nursing homes.

These are the people with the most severe disease. They're the people who are most likely to have psychosis. Psychosis rates are far, far higher in people with Alzheimer's disease in nursing homes than they are amongst individuals at home. They're the people who have the biggest problems tolerating currently available atypical antipsychotics and have the biggest adverse effect.

So I think the potential for benefit in terms of improving symptoms, reducing distress, and reducing unnecessary harms is extremely great in that nursing home population, but that's not to take away from the important benefit of preventing

institutionalization in people living at home.

MR. DeKARSKE: Thanks, Dr. Ballard.

DR. NARENDRAN: Just as a follow-up to that, I get that point, but how do you then divorce agitation and aggression from psychosis in a nursing home population? And you didn't see an improvement in that because it seems like that would be the biggest issues, is agitation and aggression, and how is that really divorced from psychosis per se in that data set?

DR. BALLARD: Clive Ballard. We applied rigorous criteria for assessing both. As part of the inclusion criteria for the 019 study, we required people to have sufficient verbal ability to be able to describe their symptoms. So if they had hallucinations, they were able to describe those. They weren't inferred from behavior. If they had delusions, they had to be able to verbalize those, and we applied rigorous criteria in order to both diagnose them and evaluate them with the NPI.

So I think it's perfectly possible in people

who are able, you have that verbal ability to assess psychotic symptoms accurately in people with pretty severe dementia, and that's been done across a number of studies.

In terms of agitation, concurrent agitation is a big problem, and 30 to 50 percent of people with psychotic symptoms in the context of Alzheimer's disease do have concurrent agitation. The evidence from the literature is that the neurobiological basis of the agitation is different to the basis of psychosis, but that psychosis is one of the factors that might impact on agitation. And although we didn't see any overall benefit in agitation, we did see that when there was a 50 percent improvement in psychosis, there was also a substantial benefit in agitation associated with that.

So improving psychosis did have a knock-on benefit in terms of reducing agitation when psychosis improved, but there are different symptoms. They have a different neurobiological underpinning, and in people with verbal ability,

these symptoms can be assessed accurately and robustly in nursing home patients.

DR. NARENDRAN: Thank you.

MR. DeKARSKE: Dr. Narendran, just as a quick follow-up, you mentioned Dr. Tariot in the context of your question about the utility in nursing homes. I just want to give Dr. Tariot just a moment to respond directly to you.

DR. TARIOT: Thank you. Pierre Tariot, consultant.

Dr. Narendran, I think you actually pointed out a flaw in my presentation. I was actually director of psychiatry at a very large long-term care facility in Rochester, New York for 20 years. We did a study evaluating the presence of neuropsychiatric disorders ourselves as opposed to chart diagnoses, and we essentially showed -- this is like a state psychiatric hospital, these settings -- half or more of the residents have dementia, and most of those folks have very prominent neuropsychiatric symptoms, including, as you point out, agitation and aggression, but also

including psychosis.

I've done many of these trials myself with NIH funding, industry funding. We have yet to find anything that's truly effective for agitation and aggression, and the best we can do is essentially put somebody into a pharmacologic straitjacket, which is just not acceptable. So in fact, for agitation and aggression, our own clinical approach is to focus on non-drug strategies as best we can and really reserve drugs when we're faced with hospitalization, and we really want to try to keep these folks out of the hospital.

So I did not mean to suggest that there isn't a role in the long-term care setting as well. That was really my main point. Thanks again.

DR. NARENDRAN: Thank you.

We have time for one last question.

Dr. Walter Dunn?

DR. W. DUNN: Hi. Walter Dunn, UCLA. This is a question for Dr. Hendrix.

In the briefing document for 045, you conducted a tipping-point simulation analysis to

mitigate the effects of the Parkinson's group to determine if the study would have been a positive just with the ADP cohorts.

Can you describe, when they talk about adding 9 events to the PDD group, do you actually mean that you increase the relapse rate for the PDD group to 11 out of 15? Then as a follow-up, can you just comment briefly on the advantages and disadvantages of this tipping-point analysis versus what the FDA did with removing the PDD group altogether from their analysis to determine if an ADP would have been significant?

DR. HENDRIX: Yes. Thank you. Suzanne Hendrix, statistical consultant.

So the purpose of this analysis was to reproduce, in as close a fashion as we can, what would have been expected for overall DRP if the PDD group hadn't been so dramatically different than the other group. And of course because the study wasn't powered within the ADP subgroups specifically, I wanted to perform an analysis that would have similar power to the original design of

the DRP study. So if we take out the PDP group in its entirety and just look at the subgroup of ADP, we lose the power of having those additional patients in the analysis.

So the goal of this analysis was to say how much did the PDD results actually drive the analysis of overall DRP, and if we were to have a more comparable hazard ratio in the PDD subgroup, would we still achieve significance overall in DRP?

So by adding the additional events, what we find is that once we add as many as five or four -- let's see, 5 events. So near the bottom, the middle of the bottom section here is what I'm looking at in the PDD group. We have 5 events added, a p-value of 0.028. Right below that, we have 6 events added, and we don't have significance anymore in the ADP subgroups, so we just have a trend. That trend is consistent with the effect that we saw for ADP as a whole, and when we then go up to the top section and look at that same corresponding row with 6 events, we have overall significance.

So the point of this was to say we don't achieve significance with ADP alone, but that's because it's underpowered, and we do achieve significance if PDD, ADP, and other were all at similar levels of hazard ratio, and then we would have gotten significance overall for DRP. So it's just another way to look at whether the study would have been significant if it had been ADP as a whole with the larger sample size and with similar hazard ratios across all of the groups put together.

DR. W. DUNN: Great. Thank you.

DR. NARENDRAN: We're a little past 11:10, so I think it's time for us to take a quick 10-minute break. Panel members, please remember that there should be no chatting or discussion of the meeting topic with other panel members during the break. We will resume at 11:20 to start with the agency presentations.

MR. DeKARSKE: Dr. Narendran?

DR. NARENDRAN: Yes?

MR. DeKARSKE: Excuse me. There were two questions during the presentation concerning the

history of the protocol for 019, and this concerns the primary endpoint. We've put together a slide that outlines the history, and we'd be happy to share just to, I think, perfectly clarify the inception of the protocol, its conduct, and up to database lock.

DR. NARENDRAN: If the agency's ok with it, maybe we can do that right before they start.

Is that ok? I want to check with them.

(Whereupon, at 11:12 a.m., a recess was taken.)

DR. NARENDRAN: Thank you, everyone. Hopefully everyone's back.

I just wanted to give the sponsor a couple minutes to address their request before we start with the FDA presentations. So if you guys want to go ahead and respond about the Study 019.

DR. TARIOT: Thank you. This is Pierre Tariot, pinch-hitting just for a moment while the team reassembles.

Could we pull up -- is it TI-72? Because we realize we've kind of not given a crisp response to

this, so I'm stalling a little bit.

Daryl, you're on.

DR. STANKOVIC: Serge Stankovic, Acadia, speaking. I want to thank Dr. Fiedorowicz and Dr. Thambisetty for asking this question. It is very important that we are absolutely clear on this point.

I want to make two points. One is the 6-week endpoint was never a subject on any protocol amendment, and it was never modified from the beginning of the trial to the end of the trial. In terms of amendments, let me just go through history very quickly.

The study protocol was approved in 2010. There were three protocol amendments to this protocols, Study 019, one in 2013, as you can see on the slide; one in 2014; and one in 2015; the last on 16th of November of 2015.

Data for this study was locked on December 2, 2016, and the data was blinded on December 5, 2016, which means the full year plus after the last protocol amendment. And above and

beyond all of that, none of these protocol amendments ever made any changes to the 6-week endpoint. So I hope that this clearly states and clarifies that there were not any changes to the endpoint and not any changes to the protocol, per se, following the database lock and the data unblinded.

I also want to say that the misunderstanding most likely comes from clinicaltrials.gov, which is involving posting often with some mistakes. And in this case, the clinical trial posting was just an error, but it doesn't have anything to do with the protocol amendments, with implementation of the protocol, or with the timing of the database lock and unblinding.

If there are any questions, I'm happy to respond, but I hope that this clarifies this on a factual basis. Thank you.

DR. THAMBISETTY: Dr. Narendran, may I make a quick response? This is Dr. Thambisetty.

DR. NARENDRAN: Sure, very quickly, please. Thank you.

DR. THAMBISETTY: Sure.

Dr. Stankovic, thanks a lot for that clarification. My concern is about the clinicaltrials.gov website, which says that there were two amendments made in July 2017 and September 2017, which is a year after the blind was broken from your slides.

So if that was an error, it might need to be corrected because that is a public record. It's something that you as a sponsor have submitted to clinicaltrials.gov, and if you in fact do side-by-side comparisons of earlier versions of the protocol, with the amended protocols in July 2017 and September 2017, you can actually see text that clearly have been deleted to say that the primary endpoint of 12 weeks was in fact changed to 6 weeks. This may be a quirk of the clinicaltrials.gov website; I do not know. But I find it a useful resource to track changes to protocol amendments that are not otherwise publicly available, which is why I referenced that source to preface my question. Thank you.

DR. NARENDRAN: Thank you. I think that kind of addresses the issue.

So we will now proceed with the FDA presentations, starting with Dr. Paul Bossie.

FDA Presentation – Paul Bossie

DR. BOSSIE: Thank you.

My name is Paul Bossie. I'm the clinical reviewer for the application. I will discuss relevant regulatory history, an overview of the design and results of Study 019 and the resubmission, and an overview of the design of Study 045. My statistics colleague, Dr. Xiang Ling, will discuss the Study 045 results and resubmission analyses before I return to provide concluding remarks.

Pimavanserin was approved in 2016 for the treatment of hallucinations and delusions associated with Parkinson's disease psychosis or PDP. At a 2008 pre-investigational new drug meeting, the applicant outlined a plan for Study 019, a phase 2, randomized, double-blind, placebo-controlled trial of pimavanserin in

subjects with Alzheimer's disease psychosis, or ADP, to serve as part of a multi-study approach to support a dementia-related psychosis indication.

At a 2017 end-of-phase 2 meeting, the agency agreed that the treatment of hallucinations and delusions associated with dementia-related psychosis was a potentially approvable indication. The agency expressed concern about basing a regulatory decision on a single randomized withdrawal study -- that is Study 045 -- but ultimately agreed that it would be acceptable as a well-controlled trial for supplement submission for the indication of hallucinations and delusions associated with dementia-related psychosis.

The agency agreed with the population as long as subjects were stratified by their current clinical diagnosis; that is dementia subtype, and noted that labeling would reflect the actual composition and response of subjects enrolled in the study. The applicant submitted the supplement in June 2020, supported by Study 045, with Study 019, and resubmitted data from Study 020, a

phase 3 study in subjects with Parkinson's disease psychosis, which included a subset of subjects with dementia.

The agency issued a complete response in April 2021, concluding that the supplemental application did not provide substantial evidence of effectiveness for the treatment of hallucinations and delusions associated with dementia-related psychosis. Although it is very important to note that Study 045 was not powered to demonstrate subgroup efficacy, an examination of dementia subgroups revealed the following observations.

Results for the Parkinson's disease dementia, or PDD, subgroup were highly nominally statistically significant. Despite being a relatively small subgroup of 35 subjects, the finding in the Parkinson's disease dementia subgroup appeared to drive the overall study results.

Again noting that the study was not powered for subgroup statistical analysis, the results for the Alzheimer's disease, or AD, subgroup were not

nominally statistically significant despite being the largest subgroup with 123 subjects. However, numeric separation of the AD group from placebo was apparent.

Too few subjects with dementia with Lewy bodies or frontotemporal dementia were included to adequately represent those subgroup responses, and there was no difference on time to relapse between pimavanserin and placebo in the vascular dementia subgroup.

The agency noted that the results of Study 045 essentially demonstrated what was already known, that pimavanserin was effective in the treatment of Parkinson's disease psychosis whether or not patients have dementia. The agency noted that the Study 045 findings suggested a differential response to pimavanserin across dementia subtypes, which called into question whether dementia-related psychosis is a useful construct for a potential indication. Finally, the agency noted concerns related to trial design and conduct with Study 019.

The applicant discussed its resubmission plans with the agency at post-complete response meetings, including the intention to change the proposed indication to the treatment of hallucinations and delusions associated with Alzheimer's disease psychosis. The agency agreed to consider the applicant's points in a resubmission but advised that an additional adequate and well-controlled study in subjects with Alzheimer s disease psychosis would likely provide the strongest data in support of a resubmission.

Now I will discuss Study 019. Study 019 was a phase 2, randomized, double-blind, placebo-controlled study of pimavanserin tartrate 40 milligrams once daily versus placebo. In its tartrate form, 40 milligrams is equivalent to the 34-milligram free-base approved dose.

The study was conducted within a network of 133 nursing homes in the United Kingdom, overseen by a single principal investigator. The 12-week treatment period was preceded by an approximately 3-week screening period, during which subjects

completed an antipsychotic washout if necessary, and caregivers were trained to provide brief psychosocial therapy to the subject a minimum of 3 times per week with the target of 5 times per week.

Per the applicant, the intention of the brief psychosocial therapy was to minimize placebo response prior to randomization, and to assure that only subjects requiring pharmacologic therapy were randomized into the study. The study enrolled 181 nursing home residents at least 50 years old, who met criteria for possible or probable Alzheimer's disease with psychosis, with baseline Mini-Mental Status Examination, or MMSE, scores between 1 and 22, inclusive.

Subjects were to have been nursing home residents for at least 4 weeks and not be confined to bed. Psychotic symptoms, including visual or auditory hallucinations, or delusions, were to have developed after the diagnosis of Alzheimer's and subjects were to have verbally communicated symptoms during the month before screening and

weekly during 2 weeks prior to baseline.

Subjects were excluded for psychotic symptoms caused by another reason such as delirium or schizophrenia. Anti-dementia drugs, that is acetylcholinesterase inhibitors and memantine, antidepressants, and anxiolytics, were permitted if doses were stable before and during the study. Subjects were randomized 1 to 1 to pimavanserin or placebo, and were stratified by baseline MMSE score and Neuropsychiatric Inventory-Nursing Home Version Psychosis Score, or NPI-NH PS, which I will describe next.

The primary endpoint was the mean change from baseline to day 43 on the NPI-NH PS. The Neuropsychiatric Inventory was developed to evaluate 12 neuropsychiatric disturbances, or domains, common in dementia such as delusions, hallucinations, agitation -- sorry. I don't know what just happened.

(Pause.)

DR. BOSSIE: Okay.

Is anyone else in the screen? I don't know

why it's the same thing.

(Pause.)

DR. BOSSIE: Sorry about that.

The Neuropsychiatric Inventory was developed to evaluate 12 neuropsychiatric disturbances, or domains, common in dementia such as delusions, hallucinations, agitations, and disinhibition.

(Pause.)

DR. BOSSIE: I apologize for the slide. I can't figure out why it's been pulled.

(Pause.)

DR. BOSSIE: Great. Thanks. Sorry about that.

The NPI-NH PS includes the delusions and hallucinations domains. The score of each item, as present, represents the product of symptom frequency in a range of 1 to 4, and severity in a range of 1 to 3, for a maximum score of 12 on each domain, with higher scores denoting worse symptoms. As the NPI-NH PS consisted of two domains, the maximum possible score is 24. A trained rater was to conduct the assessment with an appropriate

caregiver at the nursing homes.

The NPI has been used in other development programs, but the NPI-NH PS has not been used in other development programs regulated by the agency. Although the NPI-NH PS is considered an adequate endpoint for exploratory purposes regarding this context of use, the agency's Division of Clinical Outcome Assessment has noted that the developed evidence supporting its use has not been optimized. There are residual concerns with the scoring and the interpretation of group and individual differences, and limited evidence of content validity for this context of use.

The scoring algorithm, which totals the product of severity and frequency item scores for each domain, as seen in the upper-left table, yields a metric that may be difficult to interpret. Different permutations of severity and frequency can result in the same score highlighted here in the same color. For example, a severity of moderate and a frequency of often result in a score of 6, as does a severity of severe and a frequency

of sometimes.

As seen in the theoretical example in the table below, subject A's baseline delusions of moderate severity decreased to mild at end of study, but the delusion frequency of very often did not change. Conversely, their baseline hallucinations frequency of very often decreased to often at end of study, but the hallucinations severity of severe did not change. Examining the combined delusions plus hallucinations scores, the overall change from baseline to end of study is minus 7 points.

In terms of implications of subject A, changes in severity or frequency may or may not be meaningful, depending on subject and caretaker input. For example, is a reduction in hallucinations frequency from very often to often, but remaining severe considered to be meaningful improvement?

The meaningfulness of reduction in frequency when severity levels remain the same in terms of impact on subjects or caregivers may be unclear,

for example. Subject B began with mild delusions at baseline, occurring sometimes, that remitted by the end of study. Subject B had severe hallucinations that occurred often at baseline, which decreased to moderate severity at the end of study with no change in frequency.

Examining the combined delusions plus hallucinations scores, the overall change from baseline at the end of study is minus 5 points. In terms of implications for subject B, this 5-point change may or may not be considered meaningful because mild delusions were remitted while hallucinations decreased in severity but not frequency.

Additional information, such as more qualitative studies of the endpoint with feedback from patients and caregivers, could help provide understanding of the clinical meaningfulness of the results.

Missing evidence for content validity includes research within the development program to provide evidence of content validity or a

comprehensive review of the literature with a summary focus on how the items measure the targeted concept of interest; that is hallucinations and delusions in the Alzheimer's population. There are overall gaps in psychometric evidence in the literature.

The caretaker's rating of hallucinations or delusions may not reflect the entirety of the patient's experience because certain aspects of psychosis are not explicitly presented in the respective subquestions.

Secondary endpoints include the Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change, or ADCS-CGIC, rating at day 43. As with other CGIC scales, the rater is asked to rate the subject's functioning relative to the baseline interview using a standardized 7-point scale from 1, marked improvement, to 7, marked worsening. Other secondary endpoints included the change from baseline to day 43 on two other NPI-NH domains, on the Cohen-Mansfield Agitation Inventory-Short Form, or CMAI-SF, total score, and

on three of its subdomains.

The CMAI-SF is a 14-item instrument assessing the frequency of manifestations of agitation in the elderly, based on directly observable behaviors, including physically and verbally aggressive behaviors within the previous 2 weeks, with each item rated on a scale of 1, never, to 5, a few times an hour or continuous for half an hour or more. The score range is 14 to 70 points, with higher scores indicating more frequent agitation symptoms.

Relevant exploratory endpoints included analysis of the primary and secondary endpoints at time points other than day 43, including the NPI-NH PS durability of response from day 43 to day 85, the change from baseline to day 43 on the NPI-NH PS by baseline NPI-NH PS and MMSE score subgroups, and on the Alzheimer's Disease Cooperative Study-Activities of Daily Living, or ADCS-ADL, instrument total score. The caregiver-rated ADCS-ADL was an exploratory functional endpoint that includes 23 items related to subject ADLs, independent ADLs,

and functioning.

For the primary endpoint, the analysis was performed using the mixed-effect model for repeated measures, or MMRM method, in the full analysis set population. The model included the fixed effects of baseline MMSE category, baseline NPI-NH PS as continuous covariate, and treatment by visit interaction. The statistical analysis plan did not specify multiplicity adjustment for the secondary endpoints.

Among the 181 all-randomized subjects, 91 were assigned to placebo and 90 to pimavanserin. The full analysis set, or FAS, of 178 subjects included randomized subjects with both baseline and at least one post-baseline NPI-NH PS, with 91 subjects in placebo arm and 87 in the pimavanserin arm.

Of the 181 subjects randomized to the double-blind period,.80 percent in the placebo arm and 75 percent in the pimavanserin arm completed 12 weeks of double-blind treatment. The most common cause for early termination for the total

group was adverse events, followed by withdrawal by subject.

I'll provide an overview of major protocol deviations, as we will discuss these further regarding the applicant's resubmission. The most common categories of protocol deviation were related to missed study procedures, such as labs or vital signs, informed consent, and eligibility criteria. The most frequently reported eligibility criteria deviations included use of exclusionary medication at the time of randomization and enrollment without meeting criteria, and most notably, inability to confirm psychosis onset after Alzheimer's diagnosis.

Regarding medications, the applicant noted that subjects were treated by healthcare providers in nursing homes who were not involved in the study, and it was common for medications to be prescribed during the study without the knowledge or consent of the investigator. Treatment with these medications was often a deviation, including if given and discontinued pre-randomization if the

medications were not discontinued far enough before randomization on later determination.

Regarding eligibility criteria, the applicant noted that for many subjects, neither the nursing home personnel nor the medical record could provide a date of onset of psychotic symptoms. In those subjects, the date was reported as unknown or the same day as the Alzheimer's onset because it could not be confirmed if psychosis onset was after Alzheimer's onset; though the applicant reports that the investigator had determined that the subject had Alzheimer's, and there was no history of other psychotic disorder.

Treatment arms were well-balanced by sex, age, race, and ethnicity. The mean age of subjects was approximately 86 years across both arms. Approximately 80 percent of subjects were female across both arms. Race included 98 percent white subjects in the placebo arm and 93 percent white subjects in the pimavanserin arm. No subjects identified their ethnicity as Hispanic or Latino.

Although the treatment arms were well

balanced, the study population was not representative of the U.S. population in terms of racial or ethnic characteristics, being almost entirely white and entirely non-Hispanic or Latino. It is unclear how these differences between the U.S. population and the study population may affect the generalizability of the study results. Multiple analyses have found a higher risk of dementia in black and Hispanic-Latino populations than in white populations.

The treatment arms were also generally well balanced with respect to the duration of Alzheimer's and psychosis and baseline NPI-NH total scores, NPI-NH PS, MMSE, and CMAI-SF total scores. The median duration of Alzheimer's was approximately 57 months. The median duration of Alzheimer's disease psychosis was approximately 16 months. At baseline, the median NPI-NH PS was 8 on a possible range of 0 to 24, and the median CMAI-SF total score was 27 on a possible range of 14 to 70, where higher scores indicate worse symptoms on both scales.

A statistically significant treatment effect for pimavanserin versus placebo was observed on day 43 for the NPI-NH PS. The MMRM least squares mean change from baseline was minus 3.76 for pimavanserin group versus minus 1.93 for the placebo group, for a treatment difference of minus 1.84 with a p-value of 0.045. Various sensitivity analyses to explore the impact of missing outcomes yielded similar results to the primary analysis.

Although pimavanserin achieved statistical significance on the primary endpoint, I previously discussed some of the challenges associated with the interpretation of the NPI-NH PS in terms of clinical meaningfulness.

For the secondary and relevant exploratory endpoints, none of the between-group comparisons met nominal significance and demonstrated no notable numerical separation, including the ADCS-CGIC, the CMAI-SF total score, or the ADCS-ADL total score. Pimavanserin did not separate from placebo on the NPI-NH PS at day 64 or day 85, as

seen in this figure.

The figure displays the least squares mean change from baseline on the NPI-NH PS primary efficacy measure over the 12-week treatment period. The treatment effect appeared largest at day 43 but diminished afterwards. Placebo response at day 43 was notable compared to other time points and appeared to increase the treatment difference.

Overall, the lack of support from the secondary efficacy endpoints and the exploratory analyses that do not show discernible differences on the NPI-NH PS at day 64 or day 85 raised the question of whether the treatment difference of day 43 is a chance finding -- for example, a sudden one-time worsening in placebo group -- or questions about the durability of effect.

In the resubmission, the applicant responded to the study design and conduct concerns outlined in the agency's complete response letter regarding Study 019. At this time, the agency has concluded that Study 019 is an adequate and well-controlled trial suitable for regulatory decision making,

however, as noted previously, there are limitations of the primary NPI-NH instrument, making interpretation of the primary result somewhat challenging.

Regarding study conduct, the Office of Scientific Investigations, or OSI, conducted an inspection of the applicant during the initial supplement submission rather than an inspection of the United Kingdom study site because of COVID-19-related limitations.

Based on the findings from the applicant inspection, OSI had concerns about data reliability because of the number of protocol deviations, some of which could potentially impact whether the method of selection of subjects provides adequate assurance that they have the disease or condition being studied.

As described previously, those eligibility violations principally involved subjects who did not have clear documentation that psychotic symptoms developed after Alzheimer's diagnosis had been established, or subjects who received

exclusionary medications at the time of randomization.

The applicant has noted that the proportion of subjects with issues related to documentation of diagnosis, or that received exclusionary medications, was balanced between the treatment groups. The applicant acknowledged that there were difficulties establishing the date of Alzheimer's diagnosis for some subjects but pointed out that other eligibility criteria excluded subjects with psychosis caused by other conditions such as delirium or schizophrenia. The applicant also represented per-protocol analysis results to demonstrate the impact of protocol deviations.

Here, the left side of the table displays the per-protocol set analysis, and the right side of the table displays the statistical reviewer's analysis that I'll discuss in a moment. As you can see on the left side of the table, the per-protocol set results were in favor of pimavanserin with a treatment effect estimate of minus 3.31 and a p-value of 0.006, compared to the primary analysis

treatment effect estimate of minus 1.84, with a p-value of 0.045.

As seen on the right side of the table, the statistical reviewer repeated the primary analysis on the non-per-protocol analysis set; that is those subjects who were randomized but were not in the per-protocol analysis set.

The results showed a treatment effect estimate of minus 0.65 for a nominal p-value of 0.648. The decrease in the treatment effect estimate raises questions about the Applicant's contention that the protocol violations should not have affected the results.

Of note, almost 47 percent of subjects were excluded in the per-protocol analysis. Such a large number of randomized subjects excluded from the analysis could lead to selection bias and exaggeration of treatment effect. Results of this subgroup may not be generalizable to the intended population. The full analysis set should be used to assess treatment effect rather than the per-protocol set.

Overall, the agency anticipates that we will be able to rely upon the data from Study 019 for regulatory decision making, based on the balanced distribution of the protocol deviations and after examining the nature of the deviations and mitigating factors such as other eligibility criteria.

In summary, the results of Study 019 demonstrated a statistically significant result on the primary endpoint change from baseline to day 43 on the NPI-NH PS. The endpoint appears to have face validity for a phase 2 exploratory study, but the developmental evidence supporting its use is not optimized. The clinical meaningfulness of the treatment difference may be difficult to interpret and would benefit from support by other outcome assessments.

On secondary and exploratory endpoints, there was a lack of notable separation from placebo, whether a nominal statistical significance or a numerical, so we lack evidence in the secondary or exploratory endpoints to assist our

interpretation of the primary endpoint. The lack of discernible differences on the NPI-NH PS primary outcome measure after day 43 raises questions of whether the difference of day 43 is a chance finding or about the durability of effect.

Moving on to Study 045, Study 045 was a phase 3, randomized, double-blind placebo-controlled, multicenter, randomized withdrawal study of pimavanserin 34 milligrams once daily versus placebo, with potential dose adjustment to 20 milligrams described on a later slide.

Subjects were screened across 101 international sites, including 27 in the United States. The 3 to 35-day screening period included brief psychosocial therapy and an antipsychotic washout if necessary, as in Study 019. A 12-week open-label period was followed by an up-to-26-week double-blind period.

Eligible subjects were 50 to 90 years old, inclusive, with all-cause dementia and clinical criteria for dementia subtype; with a baseline MMSE score between 6 and 24, inclusive; and with

psychosis symptoms for at least 2 months. Subtypes included Alzheimer's dementia; Parkinson's disease dementia; dementia with Lewy bodies; frontotemporal dementia spectrum disorders; and vascular dementia.

Subjects must have had screening and baseline scores on the scale for the assessment of positive symptoms, hallucinations plus delusions, or SAPS-H+D, of at least 10, including scores on Hallucinations and Delusions global items of at least 4; and a score on a Clinical Global Impression of Severity, or CGI-S, of at least 4, moderately ill.

The full 34-item SAPS was designed to measure hallucinations, delusions, abnormalities in language and behavior, and disordered thought processes. This study used the 20 items from the Hallucinations and Delusions subscales, which include global ratings of the severity of each. Each item is rated on a 6-point severity scale from 0, none to 5, severe, for a maximum score of 100 on the two subscales, with higher scores denoting more severe symptoms.

As in Study 019, subjects were excluded for other causes of psychosis such as delirium and schizophrenia. As in Study 019, anti-dementia drugs, antidepressants, anxiolytics were permitted if stable before and during the study. No requirement for stability for anti-Parkinson's dopaminergic agents was included.

After the first week of the 12-week open-label period, subjects were permitted to decrease the dose to 20 milligrams for tolerability and re-increase at 34 milligrams for efficacy, at any scheduled or unscheduled visit until week 4, at which point the dose remained stable.

To enter the double-blind randomized withdrawal period at week 12, subjects had to meet both response criteria at weeks 8 and 12, and remain otherwise eligible. If not, they were withdrawn and entered the safety follow-up period. The response criteria required at weeks 8 and 12 included at least a 30 percent improvement on the SAPS-H+D and Clinical Global Impressions Improvement or CGI-I score of 1, very much

improved, or 2, much improved, relative to baseline.

Responders were randomized 1 to 1, stratified by dementia subtype and region. During the double blind, subjects were assessed for relapse of psychosis regularly, as well as at unscheduled visits and contacts. Subjects were considered to have relapsed if, compared to their double-blind baseline, they demonstrated any of the following: at least a 30 percent worsening on the SAPS-H+D and CGI-I score of 6, much worse, or 7, very much worse; if they were treated with other antipsychotics for dementia-related psychosis; if they stopped drug or withdrew for lack of efficacy; or if they were hospitalized for worsening psychosis. An independent adjudication committee reviewed all termination cases that occurred before the study discontinuation date to determine if protocol-defined relapse criteria were met.

The primary endpoint was time from randomization to relapse in the double-blind period. The secondary endpoint was time from

randomization to discontinuation from the double-blind period for any reason. Exploratory endpoints relevant to the applicant's resubmission included the SAPS-H+D total score and separate Hallucinations and Delusions domain scores.

The total number of relapse events required at the final analysis was 75. Sample size calculation was based on a placebo relapse rate of 60 percent over 26 weeks and a pimavanserin relapse rate of 35 percent over twenty 26 weeks, for a hazard ratio of 0.47; a dropout rate of 25 percent over 26 weeks; an overall two-sided alpha of 0.05; and a one-sided O'Brien-Fleming stopping boundary of 0.0033 for the interim analysis when half of total planned relapse events occurred. The primary endpoint was analyzed with the Cox regression model with covariates for treatment group, dementia subtype, and region.

Of the 392 subjects enrolled in the open-label period, 351 subjects completed or discontinued from the open-label period and 41 were still ongoing in the open-label period at the time

of study discontinuation, following interim analysis. Among the 351 subjects, 217, or 62 percent, met response criteria at weeks 8 and 12, and were randomized to the double-blind period.

The most common reason for early termination during the open-label period was lack of response for 20 percent of subjects, followed by discontinuation for adverse events for 8 percent of subjects. In terms of open-label responses, as you can see here in the left column, within each dementia subtype, roughly 60 percent of subjects with Alzheimer's met the response criteria and were randomized, and roughly 71 percent of the subjects of PDD met the response criteria and were randomized.

In the right column, roughly 19 percent of subjects with Alzheimer's were considered to have a complete response, defined as 100 percent symptom reduction on the SAPS-H+D and a CGI-I of 1 or 2, and roughly 27 percent of subjects with PDD had a complete response.

In the open-label period in both

double-blind arms, subjects included roughly 60 percent females, mean age was roughly 74 years, race was almost entirely white, and ethnicity was roughly 76 percent non-Hispanic or Latino. In terms of racial characteristics, the study population was not representative of the U.S. population, being almost entirely white.

Generally, dementia subtype distribution was similar between open-label and double-blind periods in both double-blind arms, with approximately 63 percent of subjects with Alzheimer's and 19 percent with PDD in the double-blind period.

Double-blind baseline mean MMSE scores were generally similar between the arms. Mean SAPS-H+D scores improved from open-label baseline at 24.4 to similar double-blind baselines in both arms, at 5.0 for pimavanserin and 5.2 for placebo. As a reminder, the possible range of SAPS-H+D scores are of 0 to 100.

I'll turn it over here to my statistics colleague, Dr. Xiang Ling, to discuss Study 045's efficacy results and resubmission analyses.

FDA Presentation – Xiang Ling

DR. LING: Thank you, Dr. Bossie.

My name is Xiang Ling. I'm the statistical reviewer for Study 045. I'll cover the next few slides on the statistical analysis.

Study 045 met its primary endpoint of time from randomization to relapse in the double-blind period. In accordance with the statistical analysis plan, an interim analysis was conducted after 40 relapse events had occurred. The prespecified stopping criterion was met at interim analysis because the one-sided p-value of 0.0023 was less than the O'Brien-Fleming stopping boundary of 0.0033, and the study was stopped early for efficacy. However, there are large differences in the estimates of the treatment effects in terms of hazard ratio across the dementia subtypes. Only the treatment effects in the subgroups that include PDD subjects appeared to differ from placebo, with confidence intervals excluding no effect, hazard ratio of 1.

For the AD subgroup, the confidence interval

includes a hazard ratio of 1 and is wide, indicating large statistical uncertainties about the estimated treatment effect. Additionally, the confidence intervals for the AD and the PDD subgroups did not overlap, suggesting differential treatment effect across dementia subtypes. However, it is important to note that the study was not powered to provide reliable estimates of the subgroup effects and differences.

Additionally, the exploratory analysis of the primary endpoint, excluding the PDD subset, did not meet the O'Brien-Fleming stopping boundary of 0.0033, nor the nominal one-sided significance level of 0.025. Of note, this exploratory analysis has reduced power.

In the next few slides, we'll discuss the resubmission with a focus on the analysis of the AD subgroup in accordance with the revised indication of the treatment of hallucinations and delusions associated with Alzheimer's disease psychosis. In the resubmission, the applicant asserted that there was consistency of response across dementia

subtypes. The applicant hypothesized that the PDD subgroup's smaller hazard ratio was caused by the use of dopaminergic therapy to manage motor symptoms of Parkinson's disease, which could cause or worsen psychotic symptoms.

Additionally, the applicant conducted a reanalysis of the primary and exploratory efficacy endpoints for the AD subgroup, as well as an exposure-response analysis that examines the relationship between plasma pimavanserin concentration and the primary efficacy endpoint. We'll discuss each of them in the following slides.

The applicant conducted a test for qualitative or crossover interaction, and concluded that the treatment effects are directionally consistent. However, there's apparent variation in the magnitude, though not the direction, of the treatment effect across subgroups. The treatment effects estimates are very different between the AD subgroup and the PDD subgroup, and the confidence intervals for the AD and PDD subgroups do not overlap.

We conducted an analysis that includes the interaction of the treatment by the dementia subgroup stratification factor in the primary analysis model. The result appears to show evidence about qualitative or non-crossover interaction for differential treatment effects across subgroups.

As we have seen, subgroup analysis by dementia subtype suggests differential results. In particular, there is a big difference in placebo response across subgroups, which may be due to the dopaminergic medication used according to the applicant's hypothesis. However, dopaminergic medication used was almost completely confounded with the dementia subtype.

Almost all subjects with PDD were on dopaminergic therapy, while few subjects in the non-PDD subgroup were on this therapy. Therefore, it is not possible to statistically adjust for the dopaminergic medication effect for the PDD subjects receiving placebo. Furthermore, it's unclear whether the effect of dopaminergic medication on

the risk of relapse is the only explanation for the possible difference in the treatment effect between the AD and PDD subgroups. Still, this does not affect the assessment of the treatment effect for the AD subgroup, which is the focus of the resubmission.

The prespecified primary analysis for time to relapse was based on the Cox regression model with treatment, designated dementia subtype, and region as factors for the analysis of the overall population. Both the dementia subtype and the region were stratification factors for the randomization.

The applicant conducted the modified Cox regression analysis that included four factors selected post hoc for the AD subgroup and excluded the prespecified region factor. The results showed a smaller hazard ratio of 0.475 and a smaller p-value of 0.1, compared to the prespecified primary Cox model.

There are some caveats to the post hoc analysis. The choice of covariates should be

prespecified, and post hoc data-driven analyses are difficult to interpret, and may be prone to bias. In addition, for the covariate of the baseline severity of psychosis, the applicant used an open-label baseline SAPS-H+D score instead of the double-blind baseline score, without providing justification.

Arguably, the double-blind baseline score may be more appropriate when testing the treatment effects in the double-blind period, and there's no reason to exclude region, which was a stratification factor in the prespecified covariate for the primary analysis.

We conducted a similar post hoc analysis, adjusting for the same covariates that applicant selected, except that the open-label baseline SAPS-H+D score was replaced with double-blind baseline score. In addition, we added back the prespecified region covariate. The resulting hazard ratio is similar to that of the prespecified primary model.

In summary, none of the p-values reached

nominal statistical significance. The modified model used by the applicant is not justified, and post hoc and potentially data-driven analyses are very challenging to interpret. Inference on the treatment effect should be based on the prespecified primary analysis unless in the rare situation where the primary analysis is clearly invalid, which is not the case here.

The most relevant exploratory endpoint for this study was changed from double-blind baseline in the SAPS-H+D score. The applicant conducted post hoc analysis on this endpoint for the AD subgroup using non-parametric test on ranked scores. Specifically, the applicant assigned the same best or second best rank to over half of the subjects, whose scores never worsened during the double-blind period. This analysis yielded a nominal p-value of 0.0375, however, for these subjects whose scores never worsened, there were still differences in terms of how much the SAPS-H+D scores changed from baseline. Additionally, relapses may be considered the worst outcome

regardless of the change in SAPS-H+D score.

We conducted an analysis using the same non-parametric test, but with ranks assigned differently. We assigned worse rank to subjects whoever relapsed based on the time to relapse, and assigned a better rank to those who never relapsed based on their maximum change score. This analysis yielded a nominal p-value of 0.1355.

In summary, results of the exploratory endpoints of SAPS-H+D score did not provide much additional support for efficacy.

Dr. Bossie will now present the exposure-response and concluding remarks.

FDA Presentation – Paul Bossie

DR. BOSSIE: The applicant also conducted an exposure-response analysis to evaluate the relationship between pimavanserin plasma concentrations and time to relapse in Study 045 to provide supportive evidence for efficacy. The exposure-response analysis assessed whether the efficacy difference between the Alzheimer's and PDD subgroups were associated with plasma concentration

and its variability. However, it does not appear that differences in subgroup efficacy are related to pharmacokinetic exposure differences, as exposures were similar between the Alzheimer's and PDD subgroups. Higher pharmacokinetic exposures were associated with a higher relapse-free probability for both subgroups, but the drug effect was lower for the Alzheimer's subgroup than the PDD subgroup.

In summary, Study 045 demonstrated a statistically significant result on its primary endpoint of time to relapse in the double-blind period. However, overall results appear driven primarily by the PDD subgroup, suggesting a possible differential response to pimavanserin across dementia subtypes.

It is unclear whether the effect of dopaminergic medication on the risk of relapse is the only explanation for possible differences in treatment effect between the PDD and Alzheimer's subgroups, and use of the medications was confounded by dementia subtype. Finally, post hoc

analyses demonstrated mixed results and are subject to inherent limitations.

I'll summarize the overall evidence and uncertainties to conclude.

In terms of evidence, both Study 019 and Study 045 demonstrated statistically significant results on their primary endpoints; in Study 019 on the NPI-NH PS change from baseline to day 43, and in Study 045, on the time from randomization to relapse in the double-blind period in Study 045.

In terms of uncertainties, for Study 019, the primary endpoint NPI-NH PS appears to have face validity for a phase 2 exploratory study, but the developmental evidence supporting its use is not optimized. The clinical meaningfulness of the treatment difference may be difficult to interpret and would benefit from support by other outcome assessments.

There was a lack of notable separation from placebo on secondary and exploratory endpoints, so we lack evidence to assist our interpretation of the primary endpoint, and the lack of discernible

differences in the primary outcome NPI-NH PS measure after day 43 raises questions of whether the difference of day 43 is a chance finding or about the durability of effect.

For Study 045, the primary endpoint results appear driven by the PDD subgroup for whom pimavanserin is already indicated as a population with Parkinson's disease psychosis with and without dementia. It is unclear if dopaminergic medication use is the only explanation for the subgroup efficacy difference between PDD and Alzheimer's. Post hoc analyses offer mixed results and are subject to inherent limitations.

That concludes our presentation. Thank you for your attention.

Clarifying Questions to FDA

DR. NARENDRAN: We will now take clarifying questions for the agency. Please use the raise-hand icon to indicate that you have a question, and remember to lower your hand by clicking the raise-hand icon once again after you've asked your question. When acknowledged,

please remember to state your name for the record before you speak, and direct your question to a specific presenter, if you can. If you wish for a specific slide to be displayed, please let us know the slide number, if possible.

Finally, it would be helpful to acknowledge the end of your question with a thank you, and end of your follow-up question with, "That is all for my questions," so we can move on to the next panel member.

The first question is from Dr. Follmann.

DR. FOLLMANN: Yes. Thanks.

I had a question about the effect of dopaminergic medication. I look at this, and I see that you have a very small p-value saying there's a difference in the treatment effect between the PDD and AD groups. That's an important result, and whether or not that is driven -- I mean, it's driven by the PDD group, but whether or not that is further caused or driven by dopaminergic medication, why does that matter? And if you concluded it was entirely due to dopaminergic

medication, would that change your conclusions? It seems to me you'd still have essentially an underpowered study in the AD group. Over.

DR. FARCHIONE: Hi. This is Tiffany Farchione, the director of the division. I think the issue here is that it seems like a reasonable explanation to say that if you have a dopaminergic medication on board, that potentially when the pimavanserin is withdrawn, that that could drive a faster relapse of psychotic symptoms.

Unfortunately, that's a hypothesis. We aren't able to say one way or the other, based on the data that we have available. It does seem like a reasonable hypothesis, but we can't answer that question with any kind of certainty at this point.

DR. FOLLMANN: I mean, even if you knew this hypothesis was true, how would I interpret the effect in the AD group differently than what it is? Which is sort of marginal or not really significant and underpowered.

DR. FARCHIONE: Right. Well, that's one of the questions that we're really asking the

committee to opine on in terms of the strength of the data that we have available to us. I think that, ultimately, the best way to respond to that would be to have a study in the Alzheimer's only groups, but we don't have that at the moment.

But we do have a package available that has some evidence for us to review. These are things that we agreed would be review issues at the time of resubmission. But it does add a layer of uncertainty, so we're certainly interested in the committee's opinions about the overall strength of that data.

DR. FOLLMANN: Yes. Thank you. That's all I have.

DR. NARENDRAN: Our next question is from Dr. Thambisetty.

DR. THAMBISETTY: Thank you, Dr. Narendran. Madhav Thambisetty from the NIH.

The FDA sent in its complete response letter in April 2021 it did not consider Study 019 to be adequate and well controlled. In the Type A review meeting in June 2021, they advised the sponsor to

perform a new study of specific dementia populations; example, Alzheimer's disease. This advice was again reiterated in December 2021 in the Type C guidance meeting where, again, the agency continued to advise the sponsor that an additional adequate and well-controlled study in AD psychosis would likely provide the strongest data and support of a resubmission.

With all of the analysis presented today, Study 019, in my opinion, still remains not adequate and not well controlled. The most substantial analysis presented to support Study 019 in the resubmission to me looks as if it consists of throwing out 47 percent of data from protocol violators, and then showing that there is a large treatment effect, which to me is not valid in any way because you cannot throw out nearly half of the data of randomized participants to support the analysis. And the fact that that seems to be the only substantial analysis in the resubmission in support of 019, to me, seems quite inadequate.

Now, does the FDA believe that the

resubmission analysis, excluding 47 percent of the data, now render Study 019 adequate and well controlled? Because that is not entirely clear to me. Thank you.

DR. FARCHIONE: This is Tiffany Farchione again. It's not the per-protocol analysis that renders it adequate and well controlled; it was the deeper examination of the nature of the violations and the balance of the protocol deviations across the two groups. So we're still looking at the overall results from the full analysis set, but in following up on some of those individual deviations, we're reassured about the quality of the data.

DR. NARENDRAN: The next questions is Dr. Walter Dunn.

DR. W. DUNN: Hi. Walter Dunn, UCLA. This is a question for Dr. Bossie about Study 019, so it's two questions about it.

Number one, there's been discussion about the lack of racial and ethnic representation in terms of generalizability to the U.S. population.

Has there been a precedent in the FDA about accepting the result of a trial that was conducted exclusively outside the U.S. for an acute phase treatment study, supporting either supplemental or initial novel drug approval?

Then the second question also relates to 019. How often do you see protocol deviations in the 50 to 65 percent range? Obviously, you noted that it's quite high but, generally, what's the baseline that you see across your other studies?

DR. FARCHIONE: Quickly. This is Dr. Farchione again. I know you directed that towards Dr. Bossie, but perhaps that would be a better question for Dr. Dunn, considering his broader perspective of agency precedent.

DR. W. DUNN: Sure, of course. Thank you.

DR. B. DUNN: Sure. This is Dr. Dunn, FDA, and just unmuting.

To the first question, I want to make sure I've got those in order since they were addressed to Dr. Bossie. Your first question was about basing approvals on foreign data, essentially?

DR. W. DUNN: Correct, or any foreign population, non-U.S. population.

DR. B. DUNN: Yes. At a high level, it's easy to answer that as yes. We are able to base approvals and considerations of data on foreign data. We do need to work with the sponsor to understand the applicability of the foreign data to the domestic population. And as you heard in Dr. Bossie's presentation, some of the characteristics of that population obviously differ from our overall demographic makeup.

Quite honestly, and sadly, that's not different than many of our domestic trials as well, but as I think we all know, this is an area of tremendous focus. But we do routinely encounter data from non-domestic or ex-U.S. sources. As long as there's no scientific reason to believe that those data are inapplicable to our population, we can rely on them for a regulatory action.

DR. W. DUNN: Thank you.

Then regarding the protocol deviation rates of 50 to 65 percent in 019?

DR. B. DUNN: Oh, right. The second part of your question, it's less about the rate. I don't know that anybody on the team is going to have those data at their fingertips in terms of a comprehensive analysis of what is typically seen. I think it's about the character and understanding the potential impact.

I think you heard some presentations from the team pretty clearly discussing this, and Dr. Bossie and Dr. Ling can refer you back to the slides for this to discuss, but it seems that the team has looked at this, and felt that the character -- and notwithstanding their quantitative counts, but the character of the deviations has been considered in some detail internally, and I think you heard the team's assessment that the study is suitable for consideration.

It's the primary study that offers for support of the Alzheimer's disease population, and it won. It's a positive study on its endpoint. So the question for the committee is really the same question that we're facing here, which is what is

the persuasiveness of the data that are provided by the sponsor?

They do have a study in Alzheimer's disease; it's Study 019, and you've heard some discussion about the character of that study, and they have some support from other studies. And we also explore studies to sort out how much supportive evidence comes from within a study or from some other sources of data.

So you're presented with the same things that we're thinking about. We're trying to sort out what that primary source of evidence is and what else might support it. You heard from the team about some of the issues related to the secondary endpoints in that study and how those might play a role. But Study 019 in Alzheimer's patients did win, and those deviations are not felt to detract from that by the team at this point.

DR. W. DUNN: Thank you.

DR. NARENDRAN: Our next question is from Dr. Iyengar.

DR. IYENGAR: Thank you. I guess my

question is basically this. One of the features of randomized withdrawal design is that because only responders are included at the second stage, the treatment effect is generally believed to be overestimated. There's a bias inherent to the design.

Did anyone, either at the FDA or Acadia, do any sort of assessment of what the magnitude of that bias might be? That's my question. I'm done.

DR. FARCHIONE: This is Dr. Farchione again. What kind of analysis would you have in mind in terms of evaluating that?

DR. IYENGAR: I guess some sort of simulation study -- perhaps using some of the Study 019 data to get an estimate of an effect, and then use that in a simulation study to assess what the magnitude of the bias might be in Study 045.

I know that this is fuzzy, but one of the things that I've heard repeatedly about randomized withdrawal designs is we expect it to be biased in favor of the treatment. I've just never heard about, okay, how biased is it, and that's all I'm

asking at this point.

DR. FARCHIONE: Right. I don't believe that anyone on our team has done an analysis of that kind. I don't know if the applicant has anything to add to that.

DR. IYENGAR: Okay. Thank you.

DR. NARENDRAN: The next question is from Ms. Witczak.

MR. DeKARSKE: I'm sorry. This is Daryl DeKarske with Acadia. We had a technical difficulty.

Thanks for passing the question, Dr. Farchione. I'd ask Serge Stankovic just to comment briefly on the randomized withdrawal designed and the question around bias.

DR. STANKOVIC: Yes. Thank you. Serge Stankovic, Acadia.

A direct answer to your question, we do not have or did not perform any estimate in that regard. Frankly, we're not quite sure how would that analysis look at all, so we really don't have a response for your question either.

I would just say, in respect of the purpose of the randomized withdrawal trial, which is to evaluate maintenance of effect, we do not consider that that design is inherently biased in the demonstration of that maintenance of effect.

The second point that I would like to make is that Study 045 data on ADP, in the context of our overall submission, is supportive data to the evidence of efficacy represented with other studies, and the fact that it is overall positive in another closely related indication of dementia-related psychosis is also supportive of the evidence of efficacy. Thank you.

DR. IYENGAR: Thank you.

DR. NARENDRAN: The next question, Ms. Witczak.

MS. WITCZAK: Kim Witczak, Woodymatters, consumer rep.

In preparation for this meeting I was doing, it looks like Nuplazid has been considered an atypical antipsychotic, but it looks like the mechanism or something with the inverse agonist.

And I'm curious if you could explain what that is, that mechanism, and who determines that.

Is that something that the company determines or did the FDA determine it to be an inverse agonist?

DR. FARCHIONE: This is Dr. Farchione again. The designation of atypical antipsychotic is a limitation of our terminology in terms of medication class. It's pretty much anything that's not an old-school, Haldol type antipsychotic. Any of the newer generations from risperidone onward would be considered atypical antipsychotics, even though they all have different profiles of receptor activity.

Most of the atypical antipsychotics, the ones that are used for treatment of schizophrenia, are dopaminergic in terms of their action. So in response to your second question, yes; the company provides data from animal studies, and receptor occupancy studies, and things like that. The agency does evaluate that, and we determine what goes into the label in terms of the description of

the mechanism of action.

MS. WITCZAK: Okay.

DR. FARCHIONE: And oftentimes we are narrowing that. I can't recall on this application, in particular, if there were any differences between what the company said and what we said, but there have been occasions where a company will try to make broader claims, and we'll be like, "No, no, no, no. This is what we are going to say about the mechanism of action." So yes, it is something that we review very carefully from our nonclinical team.

MS. WITCZAK: Okay, because I was wondering if that would be -- thanks for that clarification of what is atypical. Also, then I was thinking is that what the point of differentiation is from a marketing standpoint, but it sounds like it still came from the company, and then you have to analyze it. Is that correct?

DR. FARCHIONE: Yes. I mean, the data always originates with the company, but we do our own independent evaluation of what they submit,

yes.

MS. WITCZAK: Okay. Thank you.

DR. NARENDRAN: Our next question is Dr. Cudkowicz.

DR. CUDKOWICZ: Thank you. I have two questions, first about 019. I understand that this is the trial really being considered as whether it's persuasive enough, or not, because it's in Alzheimer's.

One thing that has come up from the FDA is the concern about the primary outcome measure, and I wanted to learn a little bit more about that because we did hear from the experts that Acadia's brought in, who are treating patients, and leaders in this field, that this is a good outcome measure. And not having that much familiarity about it, I'd like to understand more about that, because this trial was positive and, in my opinion, was persuasive on that outcome measure.

So can you explain a little bit more, aside from the examples you gave, why you don't think it's a good outcome measure? What's better in this

field for psychosis in Alzheimer's?

DR. FARCHIONE: This is Dr. Farchione again. I will pass that over to David Reasner from our clinical outcome assessment group.

DR. REASNER: Yes. Thank you. David Reasner, Division of Clinical Outcome Assessment.

Well, that's a very broad question, so I will identify a couple of areas where we have an interest in additional evidence that supports the endpoint. One area is what we would describe as content validity. Often that comes from qualitative research with patients, caretakers, and treating healthcare professionals. Another area is on the quantitative side. Those would be the psychometric properties. Interesting psychometric properties might include reliability between raters, for instance.

With regard to this particular assessment, while there was qualitative research conducted, it didn't include all the areas we would typically expect when a sponsor provides a supportive evidence dossier for a particular endpoint.

With respect to the psychometric properties, we've already pointed out, to a certain extent, the difficulty of working with the total score, but in general, the psychometric properties neither correct nor undermine the core content validity of the instrument, which we believe reflects relevant and important concepts, however, the evidence package as a whole is not as broad as we would have expected.

I think, in part, there was a focus on the other targeted concepts of interest, so we have fewer assessments, secondary endpoints, secondary assessments, with which to rely on, and thank you for your question.

DR. CUDKOWICZ: Thank you.

I had just a question about 045, which I view as the supportive study. The sponsors provide some other analyses around the percent of patients with worsening symptoms by degree, and I didn't see that in the FDA's presentation or I missed it in the briefing book. I was just wondering your thoughts on that and the relevant -- this is like a

percent of people who worsened by a certain amount, comparing in the Alzheimer's group the treated versus placebo.

DR. LING: This is Xiang Ling, statistical reviewer.

DR. FARCHIONE: Thank you, Xiang Ling. I was just about to throw it over to you. Thanks.

DR. LING: We did talk about the analysis of exploratory endpoints of the SAPS-H+D score, and that plot is just another presentation. It's a discrete presentation of the SAPS-H+D score. It's descriptive in nature, but the analysis the applicant conducted related to that plot is a non-parametric test that we mentioned in their presentation.

So in our conclusion, they said that the analysis showed a nominally statistically significant result with a p-value of about 0.04, and our own analysis takes into consideration the relapses, as well as the actual maximal change score for all the patients, and our analysis resulted in a p-value of 0.1355.

DR. CUDKOWICZ: Okay. Thank you.

DR. NARENDRAN: We have another question from Dr. Walter Dunn.

DR. W. DUNN: Hi. Walter Dunn, UCLA. This question is regarding the statistical approach used by the FDA in their subsequent analyses for Study 045. This is a similar question to what I posed to Dr. Hendrix.

It looks like there were two different approaches. The FDA looked at the effect of ADP, or an ADP subgroup, by removing PDD. And as you mentioned in your presentation, Dr. Ling, you lose power, and the conclusion, at least, was that it was not significant, based off the nominal p-value. Acadia went at it a different way, where they did a tipping-point simulation, where they preserved that population that decreased the contribution from the Parkinson's group.

So can you qualitatively comment on the advantages and disadvantages of both approaches, and perhaps why the FDA shows that approach versus a similar tipping-point simulation that the sponsor

carried out? Thank you.

DR. LING: Sure. The applicant conducted a simulation to show that the overall study still had a large probability of success at the final analysis, even if this treatment effect in the PDD subgroup were simulated. However, the trial conclusion should be based on actual data instead of attenuated data.

Additionally, as the applicant's proposed indication for the resubmission is changed to ADP, we are interested in the probability of success at the final analysis for the AD subgroup instead of the overall population if in truth the treatment effects in the AD and the PDD differ. The probability of success at the final analysis for the AD subgroup is about 19 percent, assuming that treatment effect would not change over time.

This suggests that even if the trial was not stopped early, the study would have low chance of success for the AD subgroup at the completion of the study. This is due to a smaller sample size for the AD subgroup, as well as a smaller treatment

effect size for the AD estimated at the interim analysis, compared to the assumed effect size at the trial designing stage.

DR. W. DUNN: So if I understand the main differences in the two approaches, the applicant's approach would maintain a similar effect side but have a larger end, while the FDA's approach would maintain a similar effect size but have a smaller end; hence, the different conclusions.

DR. LING: That's correct. The applicant's approach, by adding more relapses, was actually an increase in number of events and increase of power, and with our analysis, the subgroup on AD will decrease the power.

DR. W. DUNN: So When the applicant added events, did they actually change the overall end or did they just switch from non-relapse to relapse?

DR. LING: The power is related to the number of events, not the number of subjects. So by increasing the number of events, it increased the study power.

DR. W. DUNN: Okay. Thank you.

DR. NARENDRAN: The next question is Dr. Follmann.

DR. FOLLMANN: Yes. Thanks. This is just a comment on the point about the bias of the randomized withdrawal study, if that's ok to talk about.

(No audible response.)

DR. FOLLMANN: Yes. An analogy is that in blood pressure trials, we'll try and identify people who are hypertensives. So you'll get people who have true high blood pressures, but they might read particularly high on that day, sort of a random high in addition to having a true high blood pressure, so if mentioned the next day, the blood pressure goes down. It's known statistically as an aggression to mean problem, and you can correct for that.

I think what's going on here is the themes are -- maybe you don't call it relapsing and remitting, but there are periods when you have psychoses, and then not. And if you grab people when they're not having psychoses, it's sort of

what you're doing during the open-label stage, and maybe they're due for a bad episode later.

So I think that's the fundamental thing. It doesn't really lead to a biased estimate of the between-group difference because you're selecting both groups during open-label, and everything's fine, but if you want to know what is the risk of relapse, then within the drug arm, then you do have this bias problem. Over.

DR. NARENDRAN: Thank you for that comment.

Our next question is Dr. Baker.

DR. BAKER: Thank you. Yes, this is Robert Baker, the industry representative. I also was going to ask about the randomized withdrawal design for Dr. Farchione or whomever she'd like to designate on this. I think we've heard a few concerns and may be accepting the last one tied to the exclusion of patients who don't respond in the open period, or even that it might be particularly biased in psychiatry.

From the perspective of industry, I was thinking about randomized withdrawal, which is an

enrichment design and has to be interpreted fairly as to how generalizable it is for the population outside the enriched cohort, but nevertheless is commonly used across therapeutic areas. And I wouldn't see a particular reason why psychiatry would be not a place for it to be used; and it looked like the division had, after some discussion with the sponsor, agreed to the approach.

So I just would be interested in your thoughts on this or confirming that in the context of other sources of evidence, it is a way to establish a drug effect.

DR. FARCHIONE: Right. This is Dr. Farchione again. I think your last comment, in terms of it being in the context of other evidence, is the key point here. In terms of standing on its own, I'm not sure that that would be appropriate. In this case, we have two other potential sources of evidence. You have the assertion from the applicant that we should be considering these as closely related conditions, so we do have the prior approval in Parkinson's disease psychosis, but then

you also have the data from Study 019.

So again, that's really why we're asking about the overall strength of the evidence. And we're ultimately going to ask the committee to discuss the contribution of Study 020 to the overall evidence base for this program, because that's really the crux of the question here, is how much can we glean from those other studies, given that this Study 045, the randomized withdrawal is really intended to be supportive data in this context, not as a primary source of evidence?

DR. BAKER: Okay. Thank you. That's helpful.

DR. NARENDRAN: The next question is Dr. Thambisetty.

(No response.)

DR. NARENDRAN: Dr. Thambisetty?

DR. THAMBISETTY: Thank you. Sorry about that. Madjav Thambisetty, NIH.

This is a question again for the FDA. It's not entirely clear to me that looking to Study 020, the initial study that formed the basis for the

approval, is valid here in this situation because the data that the FDA has presented and analyzed clearly show that the treatment response is different in AD psychosis and some PD psychosis.

So given that there is convincing evidence of a treatment by subgroup interaction to me is far more compelling that these subgroups behave differently in response to treatment than looking to Study 020 as a prior, indicating that that lends itself some support. I think the analysis presented today is very convincing, at least in my mind, that there is a very strong interaction for treatment by subgroup, and the results presented clearly show that the AD psychosis subgroup behaves entirely differently from the PD dementia subgroup.

My question was with regards to the uncertainties presented on slide 56, and I think this is important, at least in my mind, because it draws a sharp contrast between the interpretation of the results by the FDA's reviewers and those the sponsor presented earlier this morning.

So to my mind, I think slide 56 clearly

summarizes the reasons why Study 019 is not persuasive because it seems to be driven by the placebo worsening at week 6. It's not durable because the curves are not separated out at 9 and 12 weeks, and the magnitude of the effect calls into question the clinical meaningfulness, and that is well summarized in slide 56.

I just wanted to clarify with the FDA that that is in fact their position; that there is a clear difference between how they interpret the results of 019 to what the sponsor presented earlier in the morning with respect to placebo worsening, driving the results, and the lack of durability beyond week 6. Thank you.

DR. FARCHIONE: This is Dr. Farchione. As you note, these are things that we're presenting as uncertainties, stuff that we have questions about. But again, this is one of the primary reasons for seeking advice from the committee at this point, because these remain unresolved issues in the review process.

So we're very interested in your opinions,

and I think that you've stated your opinion fairly clearly at this point but, again, you'll have an opportunity to summarize in the discussion portion and with the vote.

DR. NARENDRAN: Our next question is Dr. Iyengar.

DR. IYENGAR: Sorry. I had just forgotten to put my hand down. Sorry.

DR. NARENDRAN: Thank you.

Then the next question is from Dr. Krishna.

DR. KRISHNA: Hi. This is Sonia Krishna at University of Texas, Austin. I'm also very concerned about the change at day 43. Like Dr. Thambisetty's last comment, in the morning presentation by Acadia, it was clear that that's the endpoint showing that the medicine was efficacious, and in the FDA presentation, it looks like this could be a random error.

Is there any recommendation by the FDA of how to determine whether or not this is random?

Then my second question related is, do we know how long it actually takes the medicine to

start working, if it appears that the main point is by 6 weeks and maybe not be sustained after? Thank you.

DR. FARCHIONE: This is Tiffany Farchione again. I can start with the second question, first in terms of the other source of information that we have for this would be the original pimavanserin development program in Parkinson's, where that was also a 6-week endpoint and, again, that was a very strongly positive study at the time. So I think that 6 weeks is a reasonable expectation, and the study was designed based on the assumption that we'd be able to see an effect at 6 weeks.

As for trying to determine whether it was a random blip or a real effect, this is, again, one of the reasons why we list the uncertainties that we have. We would typically look to things like related secondary endpoints or things of that nature. In this case, when we look at the secondary endpoints, we don't have additional support. Now, not all -- really, the secondaries that are really measuring the same thing are the

things looking at time point, and you can see on the various graphs what that looks like.

The other secondary endpoints would not be considered supportive either because they're not nominally statistically positive or they're measuring different things. So it makes it more difficult to really understand what that effect at day 43 is.

DR. NARENDRAN: Our next question is Dr. Walter Dunn.

DR. W. DUNN: Hi. Walter Dunn again here from UCLA, and kind of a broader question for the division and also a clarifying question.

In the briefing documents, there was not extensive mention about Study 020, although the applicant certainly emphasized the positive results from that study, and none of the voting questions or discussion questions talk about opining on the results of that in terms of influencing our decision.

Is that something that you would want us to formally consider when talking about overall

effectiveness about the evidence?

DR. FARCHIONE: This is Tiffany Farchione again. No. Study 019 was the study that supported the original approval, so we're not here to re-litigate those findings. That was a positive study. It led to the original approval. We believe that pimavanserin works well in the population for whom it's indicated right now.

The question of the relevance of Study 020 for this application has to do with the relatedness question. It's being positioned as the idea that you have a closely related condition. Like we said, there's psychosis present in both Parkinson's disease and Parkinson's with dementia, as well as in Alzheimer's.

Now, normally speaking, if you were just looking at the symptom across different disorders -- so you have two different types of dementia, you have two neurodegenerative disorders, and both of them have psychosis -- again, a priori, that's why we thought that it was reasonable to include the two populations together in a single

study because they seem related. We had no reason to believe otherwise.

Now what we're asking the committee to discuss related to that is, in that context of using it as support for this application and looking at the data from Study 045, which again was not powered to detect subgroup differences, how would you interpret that, and how would you weigh Study 020 in your overall evaluation of the evidence for this program?

DR. W. DUNN: Yes. I probably should have clarified why I asked that question. You addressed it specifically about -- yes, I think another key -- or probably the critical question for me is how related are they, ADP and PDP, and what does the current evidence tell us?

Okay. So that sounds like that's something that you would certainly want to kind of hear about our opinions as far as why we either believe or do not believe that the two conditions are either closely related or completely unrelated.

DR. FARCHIONE: Absolutely, yes. That's

what we're hoping for in the discussion. Thank you.

DR. W. DUNN: Thank you.

DR. NARENDRAN: We have another question from Dr. Thambisetty.

DR. THAMBISETTY: Thank you, Dr. Narendran. I'd like to call attention to slide 48 from the FDA's presentation, if possible. This slide refers to one of several post hoc analyses performed for Study 045.

While they are pulling up the slide, I can also reference page 33 of the applicant's submission and Figure 19, under the heading, Substantial Evidence for Effectiveness for AD Psychosis, and this is, again, relevant to the one of many post hoc analyses that were performed by the applicant. It looks as if the results that the applicant chose to present on page 33 are what are being referred to here as the applicant's modified Cox analysis. It's slide 48, the previous slide.

To me, I respect the fact that the applicant did say that all of these analyses were post hoc,

and therefore should be considered exploratory. I think that's commendable. But to me it looks as this is really an exercise in data dredging because you're using a set of post hoc covariates that were not prespecified. You're dropping a covariate that was in fact prespecified. So the region factor was a prespecified covariate that has been dropped for no reason, at least no reason in the materials that we were presented with.

So I'd like to ask if the FDA's reviewers, or other people who analyzed the data at the FDA, have any rationale presented to them by the sponsor for why this particular set of covariates were chosen; why a prespecified covariate was dropped from these analyses; and was there a list of other models that were run with other covariates that did not show comparable results?

So I'm just trying to understand the charge to the covariates used in this analysis by the applicant, and whether the FDA had any data or information as to why these were chosen. Thank you.

DR. FARCHIONE: Dr. Ling?

DR. LING: The applicant didn't provide a rationale for dropping the region factor, but they did provide a rationale for selecting the four covariates. It's basically based on literature and the results of prior studies. Maybe the applicant could add more details.

DR. THAMBISETTY: There's no reason to only choose baseline severity of psychosis during the open-label phase and not in the double-blind phase. So you've clearly shown in your own analysis, Dr. Ling, that when you use the psychosis severity in the double-blind phase, you get a different set of results. But to me, it looks as if -- the impression that I'm getting is that a variety of models were run with various permutations of covariates, and what is being shown here is the model that used the most ideal combination of covariates to show the result that we're seeing here.

DR. FARCHIONE: This is Dr. Farchione. I would like to point out that we don't have any

evidence that the applicant would have done a bunch of analyses, and then only presented the most favorable to us. Again, perhaps Acadia can comment on the specifics of why they chose this model, and talk a little bit about their model development process.

MR. DeKARSKE: Thanks, Dr. Farchione. I'll ask Dr. Suzanne Hendrix to speak a little bit further about various covariate adjusted models.

DR. HENDRIX: Thank you. Suzanne Hendrix, statistical consultant.

When we were developing the model for the covariate adjustment, we were looking at a couple of things. The first is whether there were baseline imbalances in some of these factors, and then correcting for those imbalances because of the post hoc subgroup nature of the ADP population specifically. We had achieved significant overall in the DRP, but because we weren't powered to see significance in the smaller subgroup, we knew that those baseline imbalances could make a bigger difference.

We excluded region primarily because there were smaller sample sizes in some of the regions, in four separate regions. So with those smaller sample sizes, there were some potential convergence issues with that model. When we received the response from the FDA, we went back and took their model, which they had determined with an AIC criteria, and we actually did another model where we included our baseline, which was the double-blind baseline, with their model. So we put region in the double-blind baseline, and we got actually even a better AIC, again, using the FDA's criterion for the model selection.

The main reason we use double-blind baseline -- or sorry; that we used open-label baseline rather than double-blind baseline was that at the open-label baseline, there was a lot more difference in the patients because it was prior to treatment, so they came in with all their different severities of disease, and at the double-blind baseline, everyone was on treatment, so they looked much more homogeneous.

When we put both baseline models, baseline terms in the model together, the double-blind baseline does not add significantly to the open-label baseline. But across all of these different models within the ADP group and the ADP 34-mg dose, we get consistency of the hazard ratios, with hazard ratios on the top of the figure, from 0.48 to 0.64 within the all doses group, and with 34-mg, 0.35 to 0.49.

The primary model, in my mind, based on the AIC, is actually the second from the bottom, where we have a 0.42 hazard ratio, a p-value 0.064, that had the best AIC and included both terms that the FDA had suggested and the terms that we had prespecified, or that we had designated from the literature and from past experience.

DR. NARENDRAN: Another question from Dr. Apostolova.

DR. APOSTOLOVA: It's not a question. I just, again, will postulate a bit and extend some observations from the pathology literature, which might actually explain, thus, the smaller effect

size in Alzheimer's. And that is that we know that psychosis, first of all, is one of the defining criteria for dementia with Lewy body, and also is extremely frequent in Parkinson's disease dementia. That is because it's strongly associated with the presence of Lewy bodies.

In Parkinson's disease dementia, everybody has Lewy bodies. In Alzheimer's disease and all other disorders, about 50 percent of patients have concomitant Lewy body pathology in the limbic, at a minimum, part of the brain. So that could explain why there is a little bit differential effect. We know Lewy body pathology is associated with the dopaminergic dysfunction. So I'm just offering the explanation that we don't have to anticipate a similar effect size in these disorders, based on what we know pathologically. Thank you.

DR. NARENDRAN: If there are any other questions --

(No response.)

DR. NARENDRAN: I have a quick question for Dr. Farchione.

One of the things is this NPI psychosis scale, it seems suboptimal, there are questions about content validity, and there's a very small effect. I mean, was this discussed early on? All their other trials were done with this SAPS. It seems a lot more robust and reliable.

I don't know. To what extent did this come up ahead of the trial, or was it just kind of let go because it was phase 2, and it's exploratory at that point?

DR. FARCHIONE: This is Dr. Farchione. The earliest discussions of the study design and the endpoint, everything happened back in like 2008. To give you some impression, that was before I even started at the agency. So at that time, we didn't actually even have -- the current iteration is the clinical office assessment division, but prior to that, it was something called "SEALD," which was the study endpoints and labeling development team. We didn't even have SEALD yet at that time, so really the assessment of endpoints back then was primarily one of face validity more so than

anything else.

But again, with it being initially conceptualized as an exploratory study and to be part of a larger development program, the idea of going back to look at that endpoint with greater scrutiny, even as time went on, didn't really come up. So that's sort of the history there.

DR. NARENDRAN: Thank you.

Are there any other questions? I just want to do one last screen.

Dr. Apostolova, I see your hand is still raised. Do you have another comment or question?

DR. APOSTOLOVA: No. Sorry.

DR. NARENDRAN: Okay.

If that's it, I guess we could break for lunch at 10 minutes earlier than anticipated.

We will now break for lunch. We'll reconvene at 2:00 p.m. Eastern time. Panel members, please remember that there should be no chatting or discussion of the meeting topic with other panel members during the lunch break. Additionally, you should plan to rejoin at around

1:45 to ensure that you are connected before we reconvene at 2:00. Thank you.

(Whereupon, at 1:08 p.m., a lunch recess was taken.)

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

(2:00 p.m.)

Open Public Hearing

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

For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the committee of any financial relationship that you may have with the sponsor, its product, and if known, its direct competitors. For example, this financial information may include the sponsor's payment of your travel, lodging, or other expenses in connection with your participation in this meeting.

Likewise, 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 the committee place great importance in the open public hearing process. The insights and comments provided can help the agency and the 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 for today is for the 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, please speak only when recognized by the chairperson. Thank you for your cooperation.

Speaker number 1, your audio is connected now. Will speaker number one begin and introduce yourself? Please state your name and any organization you are representing for the record.

DR. ALVA: Well, thank you very much for the opportunity. This is Dr. Gus Alva speaking. I am currently the medical director of ATP Clinical Research in Costa Mesa, California, and the medical director for the Senior Brain Health Program at Hoag Hospital in Newport Beach, as well as being an associate professor at the University of California in Riverside for the Department of Neuroscience.

I'm speaking on my own behalf, and obviously the testimony that I'm giving is as a practitioner and clinician, but I also need to let you know that I was one of the investigators in the HARMONY trial that you are reviewing right now. I sit on the scientific advisory group for Acadia Pharmaceuticals, and I lecture extensively, nationally and internationally, and obviously have had support from all of the major companies that are out there, including Acadia.

But the reason for wanting to share some thoughts with you right now is that there's a serious unmet need of patients that suffer with Alzheimer's disease, and then subsequently the

psychosis that comes about with them. Unfortunately, this is a neurodegenerative condition just like Parkinson's disease, which you've had an opportunity of reviewing, where we oftentimes see behavioral dysregulation and psychotic symptoms flare in individuals, between a third up to 40 percent of individuals thus experiencing it, and we clearly note that there's a serious ripple effect that affects not just the patient, but also their loved ones, their family members. So this is something that we see on a daily basis.

I'm a neuropsychiatrist, and my patient population is such that I see quite a few patients with both Alzheimer's, as well as Parkinson's disease, and oftentimes these conditions lead to dementia. I obviously also treat other dementias, including frontotemporal, dementia of Lewy body, and so on, and thus my interest in having served as an investigator in the HARMONY trial.

At the present time, we have a sense of urgency in that there are no approved agents to

address the psychosis associated with dementia, and unfortunately patients oftentimes get prescribed off-label antipsychotics without a proven positive benefit-risk. We note that cognition, motor function, and increased morbidity and mortality are clearly documented, based on multiple studies that have been done in this particular arena, and as a consequence of that, we need something that's been proven and safe for our patients.

The important thing right now is that there's a serious unmet need. The current medication that you are reviewing is obviously indicated for Parkinson's disease psychosis, but as has been noted by individuals working for the FDA, the overall mortality in patients that suffer with dementia, including Parkinson's, when treated with an agent like pimavanserin versus an atypical antipsychotic, and in most cases, the most common atypical antipsychotic that people reach for is quetiapine, we certainly know the higher overall morbidity and mortality in individuals being prescribed medicines that do not have an FDA

approval right now.

So obviously, the reason that I wanted to chime in is that, again, I see this on a daily basis. It's a serious important unmet medical need. We certainly note the overall risk-benefit ratio for patients is something that is important to consider.

We have the fortune of having committees like yours that can review data, and then take a look at potentially helping us. We obviously need guidance, and we obviously need individuals to peruse through all of the information as a consequence of that and garner the potential aid for many of the individuals that suffer with this illness. When someone can't trust their family members, when they're thinking that their spouse is unfair --

DR. NARENDRAN: Sorry to interrupt. We have to move on to the next speaker.

DR. ALVA: Oh. I apologize. Well, I thank you kindly for your consideration of my thoughts. Thank you.

DR. NARENDRAN: Speaker number 2, your audio is connected now. Will speaker number 2 begin and introduce yourself? Please state your name and any organization you are representing for the record.

DR. SMALL: My name is Gary Small, and I've spent most of my career studying and caring for patients suffering from Alzheimer's disease and their families. Both my mother and mother-in-law are among the approximately 6 million Americans living with the disease.

My geriatric psychiatry practice at UCLA for three decades and Hackensack Meridian Health the past two years has focused on patients with cognitive impairment. I've served as an adviser and speaker for Acadia in the past, but today I speak on my own behalf.

Most people think of Alzheimer's disease as a cognitive problem, but some of the scariest symptoms for patients and caregivers are there psychotic symptoms that afflict 30 percent of patients with the disease. These symptoms may worsen insomnia, confusion, and agitation, and

signal greater risk for nursing home placement and mortality.

Most of the family caregivers in my practice work outside the home all day and return home to care for their loved one. These two full-time jobs often lead to burnout and depression. Imagine a daughter's frustration when her mother accuses her of stealing her wallet when really her mother's wallet is simply out of sight. Despite my best efforts to explain that such paranoid thoughts shouldn't be taken personally, caregivers still feel hurt when the person they love and care for lashes out at them.

The burden of caregiving is intense, and we need to do a better job supporting caregivers. We also need safe and effective therapies to manage the symptoms and caregiver burden. Currently, there is no approved treatment for Alzheimer's related psychosis, and clinicians often prescribe off-label antipsychotics with limited efficacy. Such off-label use increases risk for further cognitive decline, infection, and even death.

There's an urgent need for approved therapies to treat the psychosis related to Alzheimer's disease. Patients, families, and caregivers need help in recognizing the onset of symptoms that are psychosis so they can better address them sooner rather than later. We also need more institutional support for caregivers, including affordable community resources, personalized medical care, education, and advocacy.

I remember how painful it was for my sisters and me to observe my mother, once a brilliant and vital force in our lives, as her mental abilities and engaging personality gradually slipped away from us. That emotional anguish was almost unbearable when she then started accusing us of stealing her clothing and jewelry as we tried our best to help. This disease impacts the entire family, and we've got to do a better job in providing support. Thank you.

DR. NARENDRAN: Thank you.

Speaker number 3, your audio is connected now. Will speaker number 3 begin and introduce

yourself? Please state your name and any organization you're representing for the record.

DR. WORZ: Good afternoon, and thank you for allowing me to speak today. My name is Chad Worz, and I'm chief executive of ASCP, the American Society of Consultant Pharmacists. ASCP represents thousands of pharmacists members managing drug therapies and improving the quality of life of geriatric patients and others in various settings, long-term care facilities, and home and community-based care.

Every day, pharmacists like me and members of ASCP are in communities helping people live better lives by effectively managing medications. This experience has led me to speak today about pimavanserin. At present, this medication is approved for Parkinson's disease psychosis. Since its approval for this indication, it has proven to be an effective and reliable tool for many clinicians and family caregivers.

I have witnessed pimavanserin improving the quality of life of patients with Parkinson's

disease psychosis. It quells harmful hallucinations and delusions that can manifest in advancing Parkinson's. I can recount stories of improvement that lessen the intensity, frequency, and sometimes eliminated those hallucinations and delusions.

One such patient I helped manage was seeing children outside her window who seemed to be in danger. The anxiety and agitation associated with the hallucination was significant, impacting everything from that person's eating and social habits to their behavioral management. Pimavanserin was able to eliminate those hallucinations and delusions from daily occurrences to monthly occurrences in a short 2-month time span.

The patient's use of supportive medications for anxiety and agitation were able to be eliminated, her eating habits improved, and her participation in social activities returned. Those kinds of real-world outcomes are common in patients treated with pimavanserin with PDP, and represent

an opportunity in people with hallucinations and delusions, and other conditions, specifically dementias.

Based on the evidence available, pimavanserin shows effectiveness and reliability for hallucinations and delusions in Alzheimer's disease. Adding this new indication would add another tool to providers working to support patients living with Alzheimer's disease and its associated neuropsychiatric symptoms like psychosis.

At present, there are no tools in this toolbox, and providers are left to select between inaction and using other medications off label and against an existing black box warning. The safety of pimavanserin and the evidence of its utility in patients with dementia make it a safe and potentially effective option in a devastating condition, which has no safe options.

An approval would bring hope to millions of patients, family members, and healthcare professionals struggling with this terrible

disease. We know that nearly half of families who turned to nursing homes do so because of their loved ones behaviors; in many cases, a direct result of their psychosis. The ability of providers and families to try this medication could allow thousands of patients to stay home longer and age in place.

As America ages, the ability of patients to remain in their homes and communities is critical. Geriatrics, like pediatrics, is a sensitive and vulnerable population. It is common and crucial that we ensure access to safe and potentially beneficial treatments where often no other safe or effective options exist.

I ask the committee to allow clinicians to practice good medicine and recommend approval, and put a potentially powerful and already proven tool in the hands of providers for patients, families, and caregivers. Thank you again for your time and attention.

DR. NARENDRAN: Thank you.

Speaker number 4, your audio is connected

now. Will speaker number 4 begin and introduce yourself? Please state your name and any organization you are representing for the record.

MS. PESCHIN: Hi, everyone. I'm Sue Peschin, and I serve as president and CEO of the Alliance for Aging Research. The alliance receives funding from the sponsor for non-branded health, education, and advocacy on neuropsychiatric symptoms of dementia, but today I'm here as a great granddaughter who loved her Bubby.

I was lucky to know my great grandmother until I was 13. We spent countless hours together at the Riverview Senior Apartments in Pittsburgh. We played cards, took walks, and visited people at the nursing home up the path from her building at the Jewish Home for the Aged.

When I was 11, my mom and I started noticing how Bubby would forget to turn the stove off or leave the water running. She slowly lost the cadence in her step and her quick wit. When my mom made the decision that Bubby needed nursing home care, it was really hard, and I think the weight of

those decisions are often not recognized. It helped that we knew many of the residents and staff there. We were allowed to sometimes help with Bubby's bathing and making sure her hair was properly done.

For a few months, Bubby would occasionally mention that she saw Hitler sneaking around the building. When constant coverage of Princess Diana's wedding was on TV, Bubby started to believe I was Princess Diana. She would kiss my hand and ask me to promise to keep kosher in the castle.

The staff taught my mom and me to go with Bubby wherever she went in her mind. They knew validation before it was a recognized thing to do. We used distraction or told her Hitler left, and that seemed to calm her. But after many months, her hallucinations and delusions came more intensely and more often, and they were harder to redirect. She'd become very scared to the point of not wanting to leave her room.

When I listen to somebody speak about psychosis as something that only needs to be

managed with behavioral techniques, I wonder to myself, has that person ever seen someone they care about thrash around, screaming in abject fear, to the point of soiling themselves and crying uncontrollably. Have they ever seen it happen multiple times or even more than once in a given day? If not, I would ask them to think about what that might be like for the person experiencing it and for the people around that person trying their best to help.

I recently saw a slide presentation against antipsychotic use that included a picture of a crying toddler. The presenter framed Alzheimer's psychosis as if it were a developmental issue that just needed proper prompting to fix. In truth, my Bubby would have been badly injured had she not been given Haldol back then.

Today, there are better therapies being developed for neuropsychiatric symptoms, but we still don't talk about symptoms like psychosis and agitation as openly as we do about memory loss, or about the importance of diagnosing and treating

them. The impact of this on care for people with Alzheimer's is significant. Moderate-to-severe neuropsychiatric symptoms diminish quality of life, and they hasten death in people with Alzheimer's. Please consider the perspectives of patients and families as you make your important decisions today, and thank you.

DR. NARENDRAN: Thank you.

Speaker number 5, your audio is connected now. Will speaker number 5 begin and introduce yourself? Please state your name and organization you're representing for the record.

MR. SCHALL: Hi. John Schall, chief executive officer of Caregiver Action Network. CAN is the nation's leading nonprofit family caregiver organization for the more than 90 million Americans who care for loved ones with chronic conditions and the frailties of old age. Acadia is one of more than 40 companies that support CAN's nonprofit mission.

On behalf of family caregivers, millions of them, I'm speaking in support of Nuplazid for the

proposed treatment of hallucinations and delusions associated with Alzheimer's disease psychosis. If approved, the drug would be the first therapy indicated for this purpose.

Alzheimer's takes a huge toll not only on our loved ones, but on us as family caregivers as well. There are 17 million family caregivers of over 6 million loved ones with Alzheimer's in the United States. Family caregivers provided 15 billion hours of unpaid care in 2020 -- $257 billion -- to people living with Alzheimer's. Family caregivers suffer higher levels of depression, face disruptions in their jobs and careers, and sacrifice financially and emotionally for their loved ones.

A recent survey of family caregivers of loved ones with dementia identified paranoid delusions, visual hallucinations, and lack of trust are common symptoms. For example, someone's mother might have a false belief that her son or daughter is stealing her personal items, and then be verbally and physically aggressive towards them.

In fact, more than three-quarters of family caregivers reported paranoid delusions as occurring at least weekly, so hallucination and delusions are much more common than many people realize.

We desperately need an FDA-approved treatment for these symptoms. Right now, with nothing else available, the off-label use of antipsychotics is sometimes prescribed, but antipsychotics often pose safety risks associated with increased mortality and hospital admissions, and they can actually worsen cognitive decline. This puts us as family caregivers in a no-win situation, having to make hard choices between doing nothing or treating our loved ones with antipsychotics, and maybe creating even greater cognitive loss.

Hallucinations and delusions don't just go away, and the problems these symptoms present are very real. Hallucinations and delusions lead to increased risk of hospitalization, they can lead our loved ones to take actions that could be harmful to themselves or their families, and they

make it difficult for us as family caregivers to care for our loved ones at home. In fact, these challenges are a leading reason why many family caregivers decide that they need to place their loved ones in a nursing home.

To finally have a therapy available, we as family caregivers will be better able to care for our loved ones at home longer, and at last give us hope that these very serious symptoms can be treated. For these reasons, we strongly support the approval of Nuplazid for hallucinations and delusions associated with Alzheimer's related psychosis. Thank you.

DR. NARENDRAN: Thank you.

Speaker number 6, your audio is connected now. Please introduce yourself and state your name and organization for the record.

(No response.)

DR. NARENDRAN: Speaker number 6?

I guess we will move to speaker number 7.

Speaker number 7, your audio is connected now.

DR. STEINBERG: Hi. I'm Dr. Karl Steinberg. I'm a long-term care geriatrician, and I've been a nursing home and hospice medical director in the San Diego area for over 25 years. Most of my patients are nursing home residents, and probably just over half of those suffer from dementia, mostly of the Alzheimer's type. I don't have any financial disclosures.

I am the immediate past president of AMDA, a national medical specialty society for nursing facility medical directors and other professionals who practice in that setting, and I take my dogs to work with me in the nursing home whenever I can.

As a front-line physician attending to many people with Alzheimer's, I want to emphasize just how devastating the psychotic symptoms of this disease can be, most importantly to the patients themselves who may be suffering extreme and distressing hallucinations or paranoid delusions, but also to their caregivers, both family and professional, and to those around them like other nursing home residents, including their roommates.

Alzheimer's psychosis and agitated behaviors related to psychosis are also very common, affecting well over 25 percent of the population at some point in their disease trajectory. There are well over a million nursing home residents in the U.S., and millions more in other congregate care settings. Symptoms can range from crying, to screaming, to actual physical violence against caregivers.

In geriatrics, we try to avoid using medications of all types whenever we can, and especially in Alzheimer's psychosis since there are no medications approved for its treatment. For Alzheimer's psychosis, we always try to use non-pharmacological interventions first; unfortunately, though, they are often ineffective. So when these patients continue to experience severe distress or present a danger to themselves or others because of psychosis, we're left with the off-label use of generally atypical antipsychotics or other medications like anticonvulsants or antidepressants.

Antipsychotic use is very highly scrutinized in nursing homes, as it should be considering the known risks of their use, including cardiovascular, metabolic, cognitive, and motor issues. And while they've been historically over-utilized, because of the scrutiny, many prescribers and facilities today are reluctant to use antipsychotics even when the patient is having severe distress. Of course, even when we do use antipsychotics, they don't always work either.

The lack of an FDA-approved medication for Alzheimer's related psychosis is a major gap for us and for our patients. There's an urgent need for us to have something in our armamentarium that we can use to alleviate the extreme, severe, and sometimes enduring distress that these unfortunate patients and those around them suffer without any understanding of what's going on, terrified and acting out in ways that would no doubt mortify them if their previous intact selves could see them in their current state.

I very much appreciate your attention and

the time today, and I ask that you please consider the severe unmet need these patients have, and don't let the good be the enemy of the perfect. I urge you to help us on the frontlines to help this vulnerable population we serve in nursing homes, dementia units, and private homes across the country, by making a medication approved and available for them, and to continue the research to find more pharmaceuticals that can make a difference in this large and growing unfortunate group of patients. Thank you so much.

DR. NARENDRAN: Thank you.

Speaker number 8, your audio is connected now. Please introduce yourself.

DR. RITTER: Good afternoon. Thank you for allowing me to speak today. My name is Aaron Ritter. I'm currently a cognitive disorder specialist at the Cleveland Clinic; Lou Ruvo Center for Brain Health in Las Vegas, Nevada. My practice is entirely focused on the care of patients with neurodegenerative disorders such as Alzheimer's disease, Parkinson's disease, Lewy body disease,

and frontotemporal dementia. My particular interest is treating the neuropsychiatric symptoms that emerge in dementia, and I have over 30 publications in my six years of practice, and have received over more than $2 million in NIH funding for various research projects.

Today I'll be speaking on behalf of the patients I treat. I have participated in clinical trials sponsored by Acadia, but have never received any direct salary, support, or financial compensation from Acadia or any of its competitors.

Simply put, the behavioral manifestations that accompany Alzheimer's disease and other related dementias are devastating, and often have a greater impact in the cognitive symptoms. In fact, many patients may not remember that they don't remember or aren't bothered that they cannot remember the date or what they ate for breakfast. But on the other hand, patients and families are acutely aware and frequently tormented by the beliefs that a spouse is cheating, a son or daughter is emptying money from a bank account, a

phantom boarder is hiding in the shadows, or the appearance of a variable cast of characters emerges from the shadows each night to watch over them as they sleep.

Research evidence is very clear that the behavioral manifestations of Alzheimer's and related dementias, including psychosis, are the primary determinants of institutionalization and the number one driver of caregiver burden.

As I'm sure you're well aware of black box warnings that accompany all of the known medications that may provide relief from psychosis in AD, and most expert commentary, rightly so, argues against the use of antipsychotics in the elderly, these recommendations however fail to acknowledge the situation in the clinic when you're presented with a family and patients in desperate need of relief from the torment of AD-related psychosis.

Clinicians such as myself are left with facing the decision of, one, treating those dreadful and terrible symptoms using dopamine

blocking antipsychotic agents, which by all accounts slowly kill patients over time; or two, offer nothing, which I believe most practitioners do. Offering no medication for ADP, however, have unintended consequences and leaves patients sick and untreated. This is precisely why many of our inpatient psychiatric wards and emergency rooms are filled with patients with dementia.

I am in the unique position of having extensive experience of using pimavanserin both clinically and in the phase 4 for patients with Parkinson's-related psychosis. I'm also in the unique position of not having it available for my patients with Alzheimer's and Lewy body disease. The bottom line is that after four years of experience with pimavanserin, I believe that to be an important and effective treatment in most cases. I would urge the committee to consider providing some weapons in our armamentarium that is currently empty. Thank you very much.

DR. NARENDRAN: Thank you.

Speaker number 9, your audio is connected

now.

DR. ZELDES: Good afternoon. I am Dr. Nina Zeldes, a senior fellow at the National Center for Health Research. We analyze scientific data to provide objective health information to patients, health professionals, and policymakers. We do not accept funding from drug companies, so I have no conflicts of interest.

As we all know, in 2018, FDA was concerned about, quote, "the number of reports of death and other serious adverse events," unquote, regarding this drug, which already carries a black box warning that there is, quote, "increased mortality in elderly patients with dementia-related psychosis," unquote. And in 2021, a study published in Urology found a statistically significant increase in hospitalizations among Parkinson's patients taking this drug compared to non-users.

Though it raises serious safety risks, the benefits of this drug would need to be substantial. There is no such evidence. Moreover, this

resubmission of a previously rejected application of broader indication relies on the same two studies which FDA previously criticized that describes Study 019 as, quote, "not an adequate and well-documented control study," unquote, and noted that there are several study design concerns and protocol deviations. And although Nuplazid showed a statistically significant improvement compared to placebo, it only translated to a treatment difference of less than 2 points on a 24-point scale.

Is that a clinically meaningful improvement for patients, especially since there is no evidence that this tiny improvement last more than a few days or weeks? The validity is questionable since statistical significance was not reached for the secondary endpoint.

FDA described Study 045 as not, quote, "powered to determine an effect in the included dementia subgroups," unquote. The results for AD patients are not statistically significant. We agree with the FDA that the proposed post hoc

analyses for this subgroup, quote, "are very challenging to interpret," unquote. For example, there is no scientific reason for the sponsor to use the open-label baseline score instead of the double-blind baseline score when testing the treatment effect on relapse in a double-blind period.

Lack of diversity is a serious problem. For example, in Study 019, only 3 patients were black and only 17 were men in the treatment group. This is not enough to draw any conclusions about either group, and together these two groups comprise close to half of Alzheimer's patients. If the sponsor had made a serious effort to recruit more men and more non-white patients, they could have done so.

My final point is that AD drugs are taken for years. The 12-week Study 019 cannot provide adequate evidence of long-term benefit or safety. To determine if the benefits outweigh the risks, we need longer placebo-controlled studies. In conclusion, I respectfully urge you to consider whether the evidence of a possible small benefit is

clinically meaningful, and if so, does it outweigh the known serious safety risks of Nuplazid? Thank you for your time.

DR. NARENDRAN: Thank you.

Speaker number 10, your audio is connected now.

DR. CALLAHAN: Hello. I am Dr. Leigh Callahan, a professor of medicine at the University of North Carolina, Chapel Hill. I have no financial relationships with the sponsor, and I'm here today representing myself. I am here because I recently lost my husband, Dr. John Winfield, to Alzheimer's disease.

John was a nationally recognized physician scientist. I watched my brilliant husband decline from this devastating disease over 10 years. There are many terrible aspects of Alzheimer's disease, but the worst symptom that John experienced was psychosis, including hallucinations, delusions, and paranoia. These symptoms were not only scary and heart-wrenching for me, but they were absolutely terrifying for John.

Let me give you a few examples. John would often think we were living in a different city, but in our same home. As the disease progressed, his suspicions and paranoia grew. Just this past December, when one of our longtime caregivers was taking down the Christmas tree and putting the ornaments away, John entered the room and became enraged, convinced Glenn was stealing the dead tree and taking our family heirlooms. He remained highly agitated, and the task had to stop.

A far more disturbing event happened a few years ago when John had his first real psychotic break. I heard crashing sounds on our screen porch. I found John surveying a room of wreckage, tables were broken, and glass shattered. I am a slight woman. I could not intercede physically, but had to convince him there were no aliens and to join me inside. It was powerful, harmfully disturbing, and crushing to see John come back to reality, survey the scene, and ask me in disbelief, "Are you telling me that I did this?"

Following this event, John's treating

physicians suggested Seroquel, and I felt strongly that this was not an acceptable choice. This would have blunted John's ability to function in general, whereas this event was transitory. We need something very different for this disease and it's dimension of psychosis.

The drug you are considering has been approved by the FDA for use in Parkinson's so patients and caregivers like me can rely on evidence of its safety in an elderly population. If you find that pimavanserin is effective in treating Alzheimer's related psychosis, this will have the potential of addressing a very high unmet need.

My primary goal was always for John to feel safe. It broke my heart that these hallucinations and delusions cost him such distress, and even terror. As you consider your task and weigh the benefits and risks of this potential therapy, please keep the dementias and psychosis in the context of this unique disease, and the experience of the patient and caregiver at the forefront of

your considerations. Thank you.

DR. NARENDRAN: Thank you.

Speaker number 11, your audio is connected now.

MR. ARTILES: Thank you. Hello. My name is Agustin Artiles. I have been a research manager with Premier Clinical Research since 2012. We are located in Miami, Florida, with the majority of our patients and families being of Hispanic origin. I'm here to share my experience working with patients and their caregivers in the HARMONY trial with pimavanserin.

In my role, I have heard many stories from caregivers, where at the beginning of the study expressed feeling scared and worried, not knowing how they would continue to care for their loved one as they became disoriented from the illness and progressed in hallucinations. Some expressed already feeling burnout and desperate either due to the behaviors or the constant supervision needed for the patient, and there are many stories I've heard about just how much this treatment has

changed patients' and families' lives.

One story I will share today is of a patient and his caregiver, his wife, because I think it will help you understand why this treatment is needed, especially in the Latin community we serve, and just how much of a difference it can make in a patient's life and in the lives of their families because ADP impacts everyone.

We saw a gentleman in his late 60s in a HARMONY trial whose wife is the only caregiver. Her husband had lost interest in family hobbies, social interactions; a complete departure from the man he once was. He needed constant supervision. His wife was experiencing her own health issues due to the burden of having to constantly provide care for her husband. She worried what would happen next if she were to fall ill.

One of the recurrent worries from caregivers is that in the Latin culture, it is not well accepted to place a family member in a long-term care facility. This forces caregivers and families to make many changes and sacrifices in their lives,

with lasting impact to support the care of the beloved family member at home.

With this gentleman and to the trial, he was unable to write a sentence or draw a simple figure. It was a challenge to have him communicate or engage in every conversation. His wife worried about episodes that might occur where she wouldn't be able to manage things on her own.

Since taking pimavanserin, this man is now engaged, listening to music, watching TV, socializing, caring for a dog, talking appropriately and coherently with his children and friends. His wife has expressed she is extremely grateful for, quote, "Giving me my life back and giving me my husband back," unquote.

These kinds of findings can be seen in many other patients in the HARMONY trial, with symptoms declining enough to allow patients to, in most cases, regain interest in their surroundings, family, hobbies, and social life, and function independently or semi-independently.

I ask you to remember what I've shared as a

treatment like pimavanserin that will help families in the Latin community care for their loved ones at home and honor their culture while sustaining their own well-being. Thank you for your time and consideration.

DR. NARENDRAN: Thank you.

Speaker number 12, your audio is connected now.

DR. GROSSBERG: Thank you very much. This is Dr. George Grossberg. I'm an academic geriatric psychiatrist, and I've spent my whole career at St. Louis University as director of the Division of Geriatric Psychiatry. I have over 25 years of clinical experience in dealing with Alzheimer's patients, as well as their family care partners.

I'm actually speaking to you this afternoon from one of our teaching nursing homes, and one of the new patients that we've been asked to see is a lovely 83-year-old woman with Alzheimer's disease, in kind of the middle to later stages, who was also accompanied by her daughter at the bedside.

Her daughter is increasingly distressed and

anxious because her mom is now starting to become accusatory toward her, as well as toward the staff, to the point where her mom believes that the staff is trying to harm her, maybe kill her. She's refusing to take her medication. She's also maybe moving toward refusing to eat, and her daughter is obviously very, very concerned.

These delusions or paranoid type symptoms, psychotic symptoms, are not rare, as you have heard, in patients with Alzheimer's disease. They significantly impact the quality of life of the patient, the family, and the professional caregivers in this kind of scenario.

Unfortunately, the current antipsychotic medications sometimes do or do not work, but they come with a lot of baggage, with a lot of side effects, particularly for patients in their 80s and 90s, as we often see with Alzheimer's disease, other Parkinsonian side effects, sedation, orthostasis, and so on and so forth; even further impairing cognition.

So there's a great need for a safe and

effective treatment that can really improve the quality of life of patients and their care partners, whether its family or professional caregivers. I'm hoping that with the development of pimavanserin, we're going to be able to fill this significantly needed void. Thank you all for listening, and thank you for the work that you're doing.

DR. NARENDRAN: Thank you.

Speaker number 13, your audio is connected now.

MS. COMER: My name is Meryl Comer. I'm the co-founder and board member of Us Against Alzheimer's. My written statement is abbreviated here to respect the time limit. I have no conflicts of interest.

For more than two decades, I cared for my husband and my mother with Alzheimer's, both of whom exhibited a range of psychoses that put them in harm's way and complicated their care. My 57-year-old husband, a respected physician and researcher at NIH, was misdiagnosed for four years

with everything from depression, to pernicious anemia, and even mad cow disease, while we were privately held captive to his paranoia, hallucinations, and delusions. The private advice to me from his attending, "You may want to get out while you can." His other advice, "Call 911 if he gets too dangerous."

Several months later, my husband was admitted to Johns Hopkins for evaluation. For the next 2 and a half months, he was confined on a locked ward where every available antipsychotic was tried, slowly titrated, and then discarded. My husband's final diagnosis read, "Alzheimer's disease with a behavior disorder," discharged to me with prescriptions that included 16 Depakote, an antiseizure medication, and 4 Ativan a day.

There was nothing left to try. The damage had been done. No facility would take him. I brought him home, and slowly weaned him off all the medication that in turn put me in harm's way. He passed two years ago, 24 years later.

My other experiences, the garden variety

psychosis suffered by my 80-year-old mother. During her early Alzheimer's paranoia, she was insistent she was being spied on by neighbors and that her personal items were being stolen, so she let no one in her house. She would scream out the window at a car to strangers to rescue her, and even called 911 to report she was being held against her will. The doctor's prescription for Seroquel never filled because we feared the long list of potential side effects more.

The reality is that whatever the FDA approves and doctors prescribe, we are left to manage the consequences. The real numbers and societal impact of psychosis and dementia are masked. As a family caregiver, we keep the secret about these behaviors, even from our adult children, to support and protect the loved one's dignity.

An FDA-approved drug, if deemed effective by this panel in treating Alzheimer's related psychosis, will help us support them at the intersection where the scaffolding of their

identity begins to fall apart due to the ravages of this fatal neurodegenerative disease with no cure. Thank you for your consideration.

DR. NARENDRAN: Thank you.

Speaker number 14, your audio is connected now.

MR. LEVINE: Good afternoon. I am Jed Levine, president emeritus of CaringKind, the heart of Alzheimer's caregiving, formerly known as the Alzheimer's Association's New York City chapter. CaringKind is the premier resource for all things related to dementia care in New York City, and I should say that Acadia is a financial supporter of CaringKind. We provide guidance and support for individuals diagnosed with Alzheimer's and related disorders, and most importantly, those who care for them. I have over 40 years of experience with this population.

Caring for a relative who's now experiencing progressive cognitive decline is unlike any other caregiving. Unless you've lived it, done it day in and day out, you don't really know what it's like,

and how exhausting and demanding it is. The challenges evolve as the disease progresses from the early stage, where the individual is still interacting in many ways as they did; to the middle stage, where the confusion, memory loss, anxiety, frustration, psychotic symptoms, and functional disabilities become more pronounced; to the end stage where the individual lost language and the ability to walk, sit up, and is dependent on someone else for all personal care.

Caregivers report that the neurobehavioral symptoms -- agitatedly asking the same question, aggression during personal care, resistance to bathing or washing hair, anxiety, pacing, sleep disruption, apathy -- are particularly distressing. And significantly adding to the stress are the psychotic features such as hallucinations and paranoid delusions.

The hallucinations, almost always visual, might not be upsetting, but often they are. Delusions, too, can be extremely troubling for the individual. I recall one member in our early stage

center who had an extremely fearful reaction to his reflection in a mirror, believing there was a threatening stranger in the home; or the former church organist who had the persistent delusion that she had to play for a service. No amount of distraction or reassurance would calm her. Common delusions include that a family member is an imposter, that the home is not their home, that a spouse is cheating or has stolen money or property.

These symptoms are a frequent feature of dementia, with some studies showing that they exist in 15 to 75 percent of patients, with delusions happening in up to 30 percent of patients. And I have heard from family caregivers who were fearful for their own safety when their person with Alzheimer's was experiencing delusions, threatening to harm them, or at times striking out at them.

We teach non-pharmacological approaches that are useful, but some individuals have persistent and resistant psychotic features that are distressing not only for that family caregiver or staff member, but for the individual themselves.

The experience of psychotic symptoms can be frightening and extremely upsetting for the person having them.

Current anti-psychotic medication, as you've heard, are often ineffective, contraindicated for use with people with dementia and can result in overly sedating the patient and have concerning adverse effects. Having a new drug to address the psychotic features will be an extremely helpful adjunct to the repertoire of non-pharmacological approaches we use now, and can greatly improve quality of life for the diagnosed individual, as well as those caring for him.

The lack of an FDA-approved antipsychotic for Alzheimer's psychosis is a substantial unmet clinical need. On behalf of the millions of individuals with Alzheimer's and their caregivers, I thank you for your consideration of the supplemental new drug application for the treatment of Alzheimer's psychosis. Thank you.

DR. NARENDRAN: Thank you.

Speaker number 15, your audio is connected

now.

DR. KIRSHNER: Yes. Hello, everyone, and thank you for allowing me to speak. My name is Howard Kirshner. I am a professor of neurology at Vanderbilt University Medical Center in Nashville. I've been the vice chair of the department and the head of the behavioral and cognitive neurology division. I also am speaking on behalf of the Clinical Neurology Society of America, which is working on a white paper on the issue of psychosis and Alzheimer's disease.

I would just say, from my own experience of 44 years of practice as an attending neurologist, that Alzheimer's is one of the most distressing diseases we deal with, and the psychotic features, the delusions and hallucinations, are the most troubling. They are the single leading cause of patients being institutionalized, which is distressing for patients and families, and then they're also a major problem in the extended-care facilities because patients are often oversedated. There is a tremendous need for a good treatment for

Alzheimer's related psychosis. There is no FDA-approved treatment as of now, as you all know, and frequently off-label use of either benzodiazepines or antipsychotic drugs, either one, is definitely harmful to the patient.

So when you consider that there are no alternatives, I think a new drug is particularly appealing. It may not be perfect. It may not have been tested in long enough courses, but it appears relatively safe, at least in short-term use, much more so than the existing medications that are tried. So I would urge, at least in the interim, approval of the drug pimavanserin, and hope for other future treatments.

I want to thank everyone on the committee for your attention to this very important issue and for the service you do every day. Thank you.

DR. NARENDRAN: Thank you.

Speaker number 16, your audio is connected now.

MS. ARCE: Good afternoon, everyone. I am Nadine Arce, and I represent our medical resource

[indiscernible] center, specifically, Dr. Navarro [ph]. We are in Miami, Florida. I am caregiver of my father, Raul [ph] Arce, who has been suffering from Alzheimer's psychosis since September 2018, when he was officially diagnosed after countless tests and medications. He was only 69 years old.

I begin by telling you that I'm a single mother of two beautiful children, a 13 year old and 3 year old. To this day, we share our life with my father, the man he was, and still is today the most loving, affectionate, and hard-working man, an example to follow up our family, and the most respected and loved being that exist. This person was always present for anything we needed, in good and bad.

In May 2015, my father began to show signs of mental decline, signs that I didn't recognize, I think because I didn't want to recognize reality. I realized that something was very wrong the day he called me because he didn't remember how to get home.

The next day, I took him to his doctor. After the appointment, everything began to change in our lives, and not for the good. Even though my best doctor put him on medication, it hurt later, and he suffered from the side effects of this medications: irritable, depressed, anxious, having trouble sleeping, and a million other things more. He also couldn't be left at home alone because of his illness.

So I decided to start to work from home to take care of him. My income decreased and my life situation also changed. I got divorced, not because of my father's situation, but I think that influenced our decision. I remain strong for my family, but I'm heartbroken from seeing such an amazing man dying day by day to such a hard and silent disease.

Thank God, in early June 2021, we were told about the pimavanserin trial. Once my father was accepted into the trial, we saw changes. This medication has helped manage my father's care and kept him at home with us where he belongs, at the

center of our family, no matter how ill he might be.

I ask you to think about my story and my father's story as you make your decision today. There are so many other families like mine out there who want to keep the people they love at home and give them the care they deserve and the life they deserve. Pimavanserin will have a great impact on the person who suffers Alzheimer's disease psychosis and their families. Thank you so much. Please make it available to us.

DR. NARENDRAN: Thank you.

Speaker number 17, your audio is connected now.

(No response.)

DR. NARENDRAN: Speaker number 17?

MS. ROYAL: Hello? Hello? Can you hear me?

DR. NARENDRAN: Yes, we can hear you.

MS. ROYAL: Okay. Thank you. I'll start again.

My name is Anita Louise Royal. I have no financial relationships to disclose. For 21 years,

I served as the Pima County public fiduciary as a lawyer, providing guardianship services to several hundreds of vulnerable adults, many of whom suffered from neurocognitive disorders. Often our goal was to preserve their self-independence, their self-determination, while ensuring their safety. Many suffered from Alzheimer's and dementias with psychotic features, including delusions and hallucinations, requiring often them to leave their own homes and be placed in residential extended-care facilities.

However, I'm not here to talk about my prior experience as a lawyer; I'm here to talk about the fact that I am one of 19 million in this country who served as a full-time caretaker for my beloved mother, who was diagnosed with dementia almost 20 years ago. I have served as her caretaker for 12 years. During that period of time, she has begun experiencing -- and actually in the last 5 or 6 years, she's begun experiencing auditory, and less often visual hallucinations.

We've tried medications. We started with

Depakote and went to Lexapro and Seroquel to deal with some of her very disruptive behaviors; nothing has worked. Thankfully, we are in the University of Colorado's senior center, where we are now getting sufficiently appropriate care for her dementia and her behaviors, however, she continues to suffer from auditory hallucinations in which she hears children crying and often loud music. When this happens, she becomes so distressed and so upset that she often tries to get out of bed, despite her limited mobility, which has resulted in her falling and having injuries.

I need as a caretaker some medication to help her from being so upset and distraught when she hears the babies crying. She thinks she has a duty to in fact help them, but she has not. I need a medication, as so many other Alzheimer's and dementia caregivers in this country do, to help our loved ones to deal with these symptoms, so that they can have more palatable, loving lives.

I just want to also thank all the rest of the speakers before me. I learned so much from

them, and I just want to thank you all for the work that you're doing on behalf of this population.

DR. NARENDRAN: Thank you.

Speaker number 18, your audio is connected now.

MS. MOREIRA: Good afternoon. My name is Jany Moreira. I am a caregiver of my mother-in-law, Amara [ph] Moreira, in [indiscernible] Medical Center. I am blessed to have a beautiful family here in Miami that really enjoys spending time together and taking a good Cuban coffee in the morning, especially my mother-in-law, Amara Moreira. This is her story.

In 2014, Amara is starting to put salt instead of sugar in the coffee and/or forget the water in the coffee maker due to depression and other psychotic symptoms. No more coffee for us. This is a small and simple thing, I know, but here I tell you about the story of Alzheimer's disease psychosis and how it changes lives and people. Due to that, I had to stop working to take care of my mother-in-law full time at home, something that

causes problems in our family. The medication she was prescribed helped a little but she continues to be depressed and sicker.

In August 2021, after no improvement, her daughter told us about the pimavanserin trial. Once my mother-in-law was accepted into that trial, we saw a big change in Amara. The loving grandmother and the dedicated mother came back to us. She pays more attention to lives today, and she gained interest in her hobbies and activities. In fact, with some assistance, of course, she has begun to make her own coffee in the morning. Her family tradition is back thanks to that medication.

So please, take my story into consideration when you are making your decision today to help many families like me who need this important treatment for family members. Thank you very much for your attention.

DR. NARENDRAN: Thank you.

Speaker number 19, your audio is connected now.

DR. CLAASSEN: Good afternoon. This is

Dr. Daniel Claassen, and I am the chief of behavioral neurology at Vanderbilt University Medical Center and professor of neurology here at Vanderbilt. I've been able to listen to the other 18 calls, and it's been quite a powerful story to hear some of the caregiver burden and some of the patients' stories.

I just wanted to give you some perspective as a physician of what things we deal with. I don't speak for Acadia. We do have some research grants from them and people in my division, but this is from my own accord.

As a clinician, especially one that takes care of those with neurodegenerative disorders, I just want to convey to you that what we do is really a practice of medicine. I know that you've probably been spending a lot of time looking at numbers and data, but I really want to give you the perspective that what we do is an art form.

Just like an artist would need to have different colors to paint a picture, I think we need to have different colors to treat psychosis,

and the colors that we have right now, especially when you think of Alzheimer's disease psychosis and other related psychoses, they're dark colors. They have a lot of side effects: Parkinsonian symptoms, weight gain, sedation, akathisia, just to name a couple of them.

I think our current practice is limited based on the labeling of pimavanserin. I'd just encourage you, from a clinician point of view, we really need new colors in our color palette, and I think pimavanserin could be an important color as we practice our art, as we partner with patients and families and try to find remedies for these terrible symptoms.

I know you have a difficult decision, and you have to make a decision based on numbers, and statistics, and data, but perhaps if you could consider how this decision really has profound implications for how me as a doctor, as my colleagues as physicians, my colleagues as nurse practitioners, how we take care of our patients, pimavanserin really does have a lot of

opportunities for us to practice better medicine, especially the lack of a titration schedule, the side effect profile, and the clinical benefits.

So I ask you as a clinician to give us a chance to practice with these new colors, and I thank you for considering this, and I thank you for your hard work and your service to make these important decisions. Thank you.

DR. NARENDRAN: Thank you.

Speaker number 20, your audio is connected now.

MR. CHAMBERS: Hello. Good afternoon. My name is Stephen Chambers. I'm a physical therapist. I live in Oakhurst, New Jersey. I've been practicing in both New York and New Jersey for the past 20 years, but I'm not speaking today in any sort of professional capacity. I have no financial disclosures or conflicts to disclose.

I'm speaking today because I know the emotional pain that the loved ones of those stricken with Alzheimer's disease endure. I support and advocate for the approval of safe

medications that minimize delusions, hallucinations, and other symptoms of Alzheimer's dementia psychosis.

My father, Chester Chambers, was diagnosed with Alzheimer's in 2014, but started showing the signs as early as 2012. We lost my father on September 8, 2021, two months prior to his 79th birthday. My father Chet was drafted into the U.S. Army within two months of graduating from college, and married my mother, his college sweetheart. After two years of service during the Vietnam War, he was honorably discharged and began his career as recruitment manager at the Social Security Administration, where he spent the next 36 years in various human resources roles.

He became a lifelong mentor and friend to many whom he hired and placed at the agency. He was also a loving and devoted son, husband, father, and friend. He was the patriarch of our family and a caregiver to us all, right up until he was unable to provide that care for us anymore, and we had to take over caring for him. He was a friend to

everyone and beloved in our community. He was truly one of the kindest people you could ever meet.

My family has a history of Alzheimer's disease. My father's mother and older brother both preceded him in death due to Alzheimer's related dementia. Despite his history, it took me and my sisters some time before we started comparing notes, and realized that he needed increasing amounts of assistance to manage his day-to-day tasks.

As the disease progressed, he began to experience delusions and hallucinations. For example, he often believed there were parties going on in his basement or extra people visiting, even when it was simply he and his home health aide alone in the house. On another occasion, he was convinced that a food delivery person had stolen his wallet when he provided a tip, although he had actually hidden the wallet in the cabinet. This incident led to me running out of the house barefoot and chasing down the delivery guy, who

assured me that there was no wallet or need for money to change hands, as I placed the order online and paid and tipped in advance.

This is just one of many instances where delusions caused extreme distress to both my father and me, and those who cared for him. My sister and I struggled with the fact that our father's delusions were just close enough to being plausible that they had to be checked out regularly, adding to the extreme levels of stress and effort required to ensure his safety and care.

These extreme levels of effort, it came to be too much, and in 2016, we had to move him to a place where he could receive around-the-clock care, which was a very difficult decision for us, as my father was a very independent, strong-willed, and highly functioning individual until that time.

Dad was prescribed Namenda and donepezil with the intent of slowing the progression of his dementia, and sertraline as well, as a mood stabilizer. We were told that there was no cure or magic bullet, and that these potentially slowed

down the inevitable. We were not [indiscernible] the option of an off-label treatment. And honestly, I think that as the disease progressed, whatever effect these medications had was minimal.

Families like mine, who love and are tasked with caring for a loved one with Alzheimer's, or some other form of dementia, are desperate for an approved treatment for Alzheimer's dementia psychosis. I hope and pray that we are not far from a cure or a successful way to minimize amyloid plaque. However, until that day comes, if there are medications like pimavanserin that can help minimize the trauma of Alzheimer's dementia psychosis, then I implore you to approve it for this purpose.

Please think of the emotional and physical distress, and frankly trauma, that this disease can inflict on those experiencing this kind of psychosis, and their families who love and care for them. If treatments like pimavanserin can help families to preserve and salvage the quality time that they have left with their loved ones, then

please make it available to patients who are experiencing Alzheimer's dementia psychosis. I thank you for your time and for allowing me to speak here today.

DR. NARENDRAN: Thank you.

Speaker number 21, your audio is connected now.

DR. FUGH-BERMAN: Good afternoon. I'm Adriane Fugh-Berman, a physician and professor at Georgetown University Medical Center and director of PharmedOut, a rational prescribing project at my university. My conflict of interest disclosure is that I'm a paid expert witness on behalf of plaintiffs in litigation regarding pharmaceutical marketing practices.

PharmedOut opposes Acadia's application to expand pimavanserin's indications to include Alzheimer's disease psychosis. Last year, the FDA rejected a broader indication for dementia-related psychosis. That rejection was correct; pimavanserin should be rejected for any subset of dementia-related psychosis.

Acadia has already begun its pre-launched marketing through its more than memory loss and more than cognition websites. It bears noting that these websites focus on dementia-related psychosis despite the black box warning on Nuplazid that states the drug should not be used for patients with dementia-related psychosis.

Tellingly, even the Alzheimer's Association, Us Against Alzheimer's, and the Alliance for Aging Research, all industry-friendly organizations that receive funding from Acadia, couldn't bring themselves to wholeheartedly back their sponsor's drugs, perhaps because that drug has the potential to kill their constituents.

You've heard the term, "unmet need" numerous times in this session, but unmet need doesn't trump data. There's always an unmet need for a symptom turned into a disease by a drug maker. The symptoms are certainly real. Psychotic episodes may accompany many diseases, including depression; bipolar disorder; Huntington's; HIV and malaria; the use of cannabis, alcohol, other recreational

drugs and prescription drugs can cause psychotic symptoms; and so can hypoglycemia. A tedious reframing of Parkinson's disease psychosis, and now Alzheimer's disease psychosis, as unique diseases benefits Acadia, but changing symptoms into diseases won't benefit patients.

At $4,173 a month, the price of the drug itself is high, but with 2.4 million vulnerable patients who could be prescribed pimavanserin outside of the controlled conditions of a trial, only a markedly effective relatively safe drug can address an unmet need. Nuplazid is not that drug.

A 2021 study by Hwang found both increased risk of hospitalization mortality with pimavanserin, and although it's been claimed that pimavanserin causes fewer deaths than other antipsychotics, a very recent study by Mosholder on Medicare beneficiaries found that it's true only in the first 6 months. After that, the risk is the same.

Antipsychotic drugs are already excessively used among vulnerable elders, especially in nursing

homes; 1 in 5 in nursing home residents are on antipsychotics. As the head of Acadia said himself, "The symptoms of dementia can overlap with symptoms of psychosis." A committee member noted that psychosis can be difficult to separate from agitation and aggression.

If any drug is approved for Alzheimer's related psychosis, the diagnosis, as well as the drug, will be legitimized. Diagnoses for this questionable condition will skyrocket, hundreds of thousands of elders will be sedated into oblivion, and many will die prematurely as a direct effect of the drug.

It's bad enough the FDA approved pimavanserin for Parkinson's disease psychosis. Please don't compound this error by recommending additional approval for an unclear diagnosis in a vulnerable population in whom pimavanserin can only cause harm. Thank you.

DR. NARENDRAN: Thank you.

We're going to give speaker number 6 -- whose audio was blocked at that time;

there were some technical difficulties -- to have an option.

Speaker number 6, your audio is connected now.

DR. WOLFE: Can you hear me now?

DR. NARENDRAN: We can hear you now.

DR. WOLFE: I'm Sidney Wolfe. I'm the founder of health research group, Public Citizen. I have no financial conflict of interest.

A study published in 2018, which now is known as Study 019, this is from the original published study, where Dr. Ballard, who is in this meeting today, said, "Pimavanserin showed efficacy in patients with Alzheimer's disease at 6 weeks, but follow-up at 12 weeks did not show significant advantage over placebo." This is in a published article four years ago.

The FDA added a few other concerns when they finally were able to get ahold of the documents from this study. The FDA inspectors had concerns about the reliability of Study 019 because of many protocol deviations, and you've seen a chart with

all of this. They principally involved subjects who did not have clear documentation that psychotic symptoms developed after AD diagnosis had been established or who received exclusionary medications at the time of randomization. As it was stated earlier, in addition to that, roughly half of the patients did not get adequate conformed consent.

So we now go to Study 045, and again, Dr. Tariot and his colleagues' paper published in the New England Journal, he stated, quote, "Longer and larger trials are required to determine the effects of pimavanserin in dementia-related psychosis. Approximately 15 percent of the patients in the trial had Parkinson's disease, which may have skewed the results in favor of pimavanserin."

The FDA has looked into this more carefully, and has data pretty much showing that whereas that subgroup who had Parkinson's disease had a statistically significant improvement -- and the data are up there -- a narrower confidence

interval, whereas the people in the AD had a non-significant improvement.

So the apparent differential effects of pimavanserin in the PDD subgroup, relative to the other dementia subgroups, was the main reason that FDA filed a complete response action in the first review, and a reason that the broad -- this is quoted from the FDA, "the broad dementia-related psychosis indication is no longer being considered."

In addition, the FDA concluded they would need a much larger sample size to be able to really find robust findings, if they exist, in the AD group. Because the trial was terminated early at the initial analysis, the conclusion can be based only on the IA results, and that concludes in, again, the briefing documents. "The study failed to demonstrate a treatment effect in the AD population."

So the voting is really on do these two studies support a conclusion that it works for AD. Given the serious flaws in both studies, we would

agree with FDA's conclusion that, quote, "the study failed to demonstrate a treatment effect in the AD population," end quote.

It's not much more than a year ago where the FDA mistakenly approved aducanumab for treating Alzheimer's disease despite the fact that the evidence was as weak, or possibly weaker, than here. So the idea of the FDA approving a drug that's been studied with a mixture of not only Alzheimer's patients, but patients who had Parkinson's disease, and the conclusion of the FDA is that's why the study overall looked good.

In the 50 years I've been going to FDA advisory committees, I've never seen a situation where someone is asking for supplementary approval --

DR. NARENDRAN: Time's up.

DR. WOLFE: -- of a drug, where the study -- I'll be done in about 10 seconds -- where the population of the study includes not only the one you were trying to approve it for, Alzheimer's disease, but also Parkinson's disease, and this

should not be approved. Thank you very much.

DR. NARENDRAN: Thank you.

The open public hearing portion of this meeting is now concluded, and we will no longer take comments from the audience.

The sponsor wanted to respond to Dr. Walter Dunn's question with a slide. So if they can do that very quickly, in 2 to 3 minutes, we would really appreciate that. So I'm going to give the sponsor a second to respond to Dr. Dunn's comments.

MR. DeKARSKE: Thank you so much, and thank you, Dr. Narendran, for giving us a few minutes to speak to Dr. Dunn's question.

Dr. Hendrix, can you please come to the mic?

DR. HENDRIX: Thank you. Suzanne Hendrix, statistical consultant.

In Study 045, among those who did not achieve stable response at both 8 and 12 weeks, and therefore were not randomized, approximately 20 to 30 percent of people had early response at 2, 4, or 8 weeks, as shown in this figure. We saw a similar pattern also in the ADP population.

The second question, we have confirmed that a hundred percent of the PD patients that did not qualify for randomization were on dopaminergic therapies, and the non-PDD patients had a low rate of dopaminergic use, which is consistent with the randomized patient population.

Thanks for the opportunity.

DR. NARENDRAN: Thank you

Dr. Dunn, do you have anything to add to this?

DR. W. DUNN: Oh, no. Thank you. Thank you very much.

Questions to the Committee and Discussion

DR. NARENDRAN: Okay. Thank you.

The committee will now turn its attention to address the task at hand, the careful consideration of data for the committee, as well as the public comments.

We will proceed with questions to the committee and panel discussion. 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.

Discussion question number one, discuss whether the evidence supports the effectiveness of pimavanserin for the treatment of hallucinations and delusions in the Alzheimer's disease psychosis population. In your discussion, comment on the strengths, limitations, and the extent to which each of the following potential sources of evidence contribute to your overall assessment of effectiveness; Study 019, Study 045, and then the prior approval of pimavanserin for the treatment of hallucinations and delusions associated with Parkinson's disease psychosis.

Are there any questions about the question from the committee to the agency, before we open this up for discussion; questions about the question?

(No response.)

DR. NARENDRAN: No questions? So I assume it's clear.

I think I would like to call on every

committee member to weigh in on their thinking on this question. So we would like to get everybody's opinion on this discussion question.

Is there anybody who wants to go first?

(No audible response.)

DR. NARENDRAN: Dr. Thambisetty, we'll start with you.

DR. THAMBISETTY: Thank you, Dr. Narendran. This is Madhav Thambisetty, NIH. I'd like to thank you for the opportunity to go first in this open discussion.

In my opinion, Study 019 remains not adequate and not well controlled, as assessed by the FDA in their complete response letter, with a substantial number of major protocol deviations, 65 percent in the placebo group and 56 percent in the pimavanserin group.

Most importantly is the separation of drug and placebo groups at week 6 as coincidence of the marked placebo group worsening. The small treatment effect at this point is not maintained at any other subsequent time point. There is also no

support of efficacy from analysis of any of the secondary or exploratory endpoints.

The use of the NPH-NH [ph] to measure the primary outcome has limited content validity, as pointed out by the FDA's analysis, and the FDA's concern with the scoring and interpretation of group and individual differences within this instrument appears to be well-founded.

With regard to Study 045, this used a randomized withdrawal design that is associated with several well-known limitations because it selects out treatment response in the open-label phase and measures the same treatment response in the double-blind phase, and this likely overestimates drug versus placebo differences in favor of the drug.

The study design also required an abrupt withdrawal of the drug, and this likely results in confounding the effects of drug withdrawal with the relapse of psychosis, thereby further undermining validity in the results from the study design.

The primary endpoint results in Study 045

are clearly driven by the PD subgroup. FDA's analysis clearly shows a strong treatment by subgroup effect, with the AD psychosis subgroup showing a lack of decent signal on the primary outcome, as well as virtually all of the secondary and [indiscernible] post hoc analyses done.

So in my opinion, Study 045 does not provide any supportive efficacy for pimavanserin in AD psychosis.

With regard to the third question about whether the prior approval is relevant here, I would go by the data that we have before that. So rather than look to the prior approval to Study 020, what I would focus on and what I would emphasize on is the actual data analysis that clearly shows a strong treatment by subgroup effects in 045, showing that these two subgroups, PD dementia and AD dementia, in fact behaved very differently in response to this drug.

Therefore, I do not think that the prior approval of pimavanserin here is relevant because the data that we have, and the analysis of the data

that we have, clearly indicates otherwise. Thank you.

DR. NARENDRAN: Thank you.

I have Dr. Cudkowicz next.

DR. CUDKOWICZ: Thank you. I'll start with Study 019. I do think it's a positive; it's definitely a positive study. It's primary, and it's supportive of an effect. It's not a perfect study. I'm reassured by the FDA, your audit and your conclusion that deviations were balanced.

The complexity of doing a study in a nursing home in people with advanced Alzheimer's, I would have been surprised not to see deviation. You never want them but, again, I'm going to go with the FDA's conclusion that it's still a study that could be considered for registration, and that those deviations were balanced, so I was concerned about the deviations.

That's a secondary [indiscernible], but they're measuring different things, and it's not that clear that this drug will work. So again, I think it has a short-term effect and may bring

faster relief to people with an awful symptom and awful disease, and I think we heard from the community how important that is. Of course it would be better if it was sustained over the 12-week period, and that's a concern, whether another study or other ways to get at that is going to be important long term.

05 [ph] is a more complicated study. It was really designed to answer the question, if this works in AD psychosis because it was broader, and it wasn't powered for that; if there are some trends for it, but it's not conclusive. So I'm putting a little less weight on that, than 019, in my thoughts about this.

If we believe that the mechanism of hallucinations and delusions is similar in Alzheimer's and Parkinson's, and the prior approval of pimavanserin is actually highly relevant, I think there's not clarity on that. We heard from some of the experts in the field that there are overlapping biologies, so there's certainly some. Whether it's all, I don't think the field actually

knows.

I do think the safety part is important from the prior [indiscernible] from pimavanserin in Parkinson's disease. My understanding from the FDA briefing booklet is that that was not something that's up for discussion or concern; it's really about the efficacy. So I think it's something safe for Parkinson's, and it's probably safe for Alzheimer's. So it's really down to whether we think it's efficacious or not. Again, I do think that Study 019 is persuasive. Thank you.

DR. NARENDRAN: Thank you, Dr. Cudkowicz.

Dr. Dunn, you're next.

DR. W. DUNN: Thank you. Walter Dunn, UCLA. So in reviewing the data and listening to discussions today, for myself there's this reoccurring theme of viewing today's issues, either from abroad all-encompassing approach versus the narrow precision perspective. Each has its merits and drawbacks.

Unfortunately, I think many of the issues before the committee today, they've been applied in

questionable context, and I'll refer back to this theme as I outline my opinions on the question proposed by the agency.

For Study 019, from a narrow consideration of the data, I agree that Study 019 is technically a win for the applicant. The additional strength of the study was that despite a considerable number of protocol deviations that actually appeared to work against the study drug, there was still an overall statistical separation from the placebo, which suggests there's a potential for a large effect from active treatment.

However, I think the totality of evidence from 019 questions a conclusion of drug efficacy. The pattern of response in the placebo arm is quite concerning, as it does suggest a chance effect at week 6, driven by worsening in the placebo arm. While I can appreciate the waxing and waning nature of psychosis in Alzheimer's dementia, I think the fact that we do not see a similar pattern in the active treatment arm suggests that the worsening of symptoms at week 6 in the placebo arm may be an

artifact completely unrelated to the disease or treatment.

However, as a side note, you actually do see a bump in symptom severity at week 9 for the drug arm, however, I don't have a good explanation as to why the waxing and waning nature of the psychosis would be, quote/unquote, "delayed" by drug treatment.

The lack of signal for all the other secondary outcomes is another concerning observation that places into question drug efficacy, and also to the question of clinical utility. The use of a primary outcome that only captures a narrow slice of symptom presentation, I think goes against what I think we should be aiming for in drug development; treatments that have an impact on functional outcomes. I agree it's challenging to win on all of your outcomes, however, I think at least a signal on the agitation and aggression domain would have made the case more compelling.

As also has already been discussed, the

differences in ethnic and racial composition of the UK study population compared to the U.S. population I think is a limitation of the study design. Obviously, this is something that occurs even within U.S. studies, and something that we should endeavor to resolve.

Regarding Study 045, I think the result from Study 045 is the prime example why we need to be working towards a more precise diagnosis in treatments for our neuropsychiatric illnesses. The field clearly appreciates that the future of medicine is about developing precision treatments, which can only occur with physician diagnoses.

So while not powered to do so, I strongly believe the results from Study 045 suggest that Parkinson's disease and Alzheimer's disease psychosis are different illnesses with differential responses to the study drug. Even within a unitary diagnosis such as schizophrenia, those of us in the field clearly believe that multiple underlying pathophysiologies across different patients drive similar clinical presentation, but with different

responses to medications.

To the question of the dopaminergic drugs driving the high relapse rate, so while that proposal is plausible, I think there is, unfortunately, no other evidence to support that conclusion. In fact, the differential response in the open-label phase between Parkinson's and Alzheimer's patients suggest otherwise.

While there was not a formal comparison, there was a higher numerical response in the Parkinson's patients compared to the Alzheimer's patients, and these were the same patients who were on the dopaminergic drugs. If that explanation were true, or partly true, I would have at least expected a numerically lower response rate in the Parkinson's disease psychosis, as their symptoms would have been complicated by the presence of dopamine agents, but in fact you actually see a better response in those patients.

Finally, to the final question about, essentially, Study 020, this leads me to the question -- I'll preface my comments by saying that

I'm only addressing the question of whether I believe the two conditions are closely related because that's, obviously, essential and necessary if I'm going to give Study 020 consideration in this new indication.

So it's ultimately up to the agency to decide what level of evidence is required for approval, but I do not believe the prior approval of pimavanserin in Parkinson's support efficacy in Alzheimer's because there's limited evidence suggesting psychosis between the two conditions is being driven by similar mechanisms or that they respond similarly to pimavanserin. In fact, as I outlined earlier, from my interpretation of Study 045, they were actually probably quite different. Thank you.

DR. NARENDRAN: Thank you.

Dr. Iyengar, you're next.

DR. IYENGAR: Thank you. Actually, my concerns were very well articulated by the earlier speakers, so I'll be a little bit brief.

I appreciate the unmet need for the ADP

patients and the attempts by Acadia to martial evidence from Studies 019 and 045, however, I see just too many problematic issues with the evidence. First, there's the unexplained blip for placebo at week 6 in Study 019; there's a demographic mismatch between the population in England and here; and there's a lack of support from secondary endpoints. There's also this issue of the treatment by subgroup interaction, which makes taking evidence from Study 020 and trying to support the current application.

In short, I think what's really needed is a well-powered study on an appropriate Alzheimer's disease psychosis sample. Thank you.

DR. NARENDRAN: Thank you.

Dr. Follmann?

DR. FOLLMANN: Yes. Thanks.

Sometimes I struggle with the decision on an advisory committee, but not today, and I think it's really just a simple and unfortunate story. Study 045 stopped early at an interim analysis, which was almost entirely driven by the result in

the PDD, and then after the study had stopped, you find this enormous statistical interaction between PDD and AD, suggesting and telling us that it's not appropriate to combine these two groups, and that we need to look at the evidence individually. So now you're left with the AD subgroup, which is simply underpowered, and while it might have had a positive numerical effect in this study, the evidence really is not there to support 019.

I thought Study 019 by itself was just significant in the ITT. It just met the p 0.05 bar. But like the comments of the FDA and a lack of a consistency across results for the secondary endpoint, and not maintaining the effect for the second half of the study, it didn't really give further support to the story of the p of 0.045 in Study 019, so I didn't find that very helpful.

In Study 045, the sponsor did many analyses, some of which showed the similarity of the response of the three different subgroups on pimavanserin, but these aren't randomized comparisons. What we really care about is the randomized comparison of

the treatment effect for the different subgroups, which is where we see this enormous effect, which allows us or ensures that we should look at the subgroups separately.

A lot of the points that I want to make, I agree a lot with what Dr. Thambisetty was saying. In particular, there were a lot of analyses that the sponsor made, but these are I think the best analyses that would support the sponsor's case, and I just found them inaggregate weak.

Then finally, Study 020, I don't think is really relevant here. I think Study 045 shows the two groups are not comparable, so I don't think that's supportive evidence. I think it's just not a very compelling story. Thank you.

DR. NARENDRAN: Thank you.

Dr. Fiedorowicz?

DR. FIEDOROWICZ: Yes. Jess Fiedorowicz, University of Ottawa. My comments are going to be much in line of what you've heard already.

(Audio feedback.)

DR. FIEDOROWICZ: Hold on. I'm getting some

feedback.

Study 019 is a phase 2 study. It included a questionably validated clinical outcome measure. The measure was significant at the 6-week time point from the protocol, although that was not appropriately publicly registered, and I do think that is an important issue.

Differences at that time point were also not consistent with surrounding time points, and that adequately was supported by secondary and exploratory endpoints, and there were some concerns about protocol deviation, some of which I think are understandable, but there are concerns nonetheless. The consent ones concern me most. The ones about the diagnosis and the timeline of that were a little less concerning because that is very difficult to tease out in clinical history.

Overall, I felt Study 019 supported the conclusions that were published in that Ballard Lancet paper, where it was published, where they said, quote, "The findings from the study suggest potential efficacy and acceptable tolerability of

pimavanserin for psychosis in Alzheimer's disease, encouraging the development of a phase 3 clinical trial program." So while Study 019 indeed supports the design of such a study and program, it falls short, in my mind, of the FDA definition of an adequate and well-controlled clinical study.

Moving on to Study 045, while the overall study was positive, it was indeed strongly influenced by the Parkinson's subgroup, where there already is an indication given. There is evidence of differential results by diagnostic group, and it's not clear to me whether this is induced by concurrent use of dopaminergic agents, and is a relevant question.

When Dr. Follmann asked the question of why does it matter, it's not clear to me that it matters. We know that there's differential response to those groups, and presumably those differences also apply to other study designs where those with Parkinson's are going to be more likely on this medicine.

The subgroup of analysis relevant to

Alzheimer's was not statistically significant. And ultimately when you look down at the raw data, it boils down to 14 relapsing with placebo versus 9 with pimavanserin for the Alzheimer's disease in FTD spectrum disorders.

On the prior approval, I think the overlap in dementia pathophysiology provides biological plausibility for consideration of that, but the results of Study 045 showing differential response ultimately question it, as others have noted. Thank you.

DR. NARENDRAN: Thank you.

Dr. Stander?

DR. STANDER: Yes. Thank you. I appreciate the opportunity to participate in this panel. I need to make sure people understand that my expertise or experience is virtually entirely as a clinician over the years, and I really appreciate a lot of the insight that's been given by the other members of the panel who have greater expertise in study design and now with this statistical interpretation. I am currently at Phoenix VA and

the faculty of University Arizona Phoenix.

I won't repeat a lot of the details from the other speakers, but I would agree that my concerns of Study 019 are some of the conclusions based on a relatively short duration, the makeup of the population, and a relatively small statistical benefit.

On Study 045, it was acknowledged that this wasn't powered to distinguish really between subgroups, and stopped early [indiscernible] for the PD population. I don't think that the efficacy prior to approval really [indiscernible].

I did want to add, though, that in listening to many of the comments, I do empathize with those individuals, because speaking from not just experience of treating patients with Alzheimer's, I did spend a considerable amount of time as a caregiver and have a mother-in-law with dementia and my mother.

So I sorely recognize the desperate need for effective treatments here, but I do think caution is necessary because a desperate need doesn't

necessarily define approval of medication that has limited or short-term benefit particularly. I also need to weigh in on what is likely to be a relatively [indiscernible]. Thank you.

DR. NARENDRAN: I think you're breaking up, Dr. Stander.

DR. STANDER: I was finished. I'm sorry.

DR. NARENDRAN: Okay. Thank you.

I heard the agency wanted to comment on the registration, clinical trials registration issue, before we continue, and I'd be happy to hand it to the agency.

DR. FARCHIONE: Thank you, Dr. Narendran.

This is Tiffany Farchione. This issue about clinicaltrials.gov and 12 weeks versus 6 weeks I think keeps coming up. I just want to make sure that that -- we have plenty of data to consider. I don't want that to color the committee's opinion.

Obviously, the company submitted their protocols to us prior to initiating any studies. From the very first submission, week 6 was listed as the endpoint for that study, so it's always been

week 6 since the beginning. So regardless of what was posted on clinicaltrials.gov, it sounds like there may have been a snafu there, but it has always been week 6. That's it.

DR. NARENDRAN: Thank you for the clarification.

Dr. Krishna, I want to give you a chance to weigh in.

DR. KRISHNA: Hi. This is Sonia Krishna.

That week 6 question is what I had brought up before, and I appreciate the clarification. If you look at that, it looks like Study 019 is positive, but I wanted more data points to confirm that, and I would like the benefit to be a bit more sustained since we do have at least the 12 weeks of data.

So it does make me more concerned about a status of placebo variation. Also, it would have been nice if any of the secondary endpoints were also positive.

I'm also curious because we have spent a long time talking about this drug labeling for PDP,

and we've talked a lot, actually, about the off-label use of atypical antipsychotics. But in the six years this drug has been out, there's no discussion about the off-label use if people have been using it for ADP, obviously understanding that we're trying to consider the labeling now. Thank you.

DR. NARENDRAN: Thank you.

Ms. Witczak?

MS. WITCZAK: Thank you. Kim Witczak, consumer rep.

First of all, I'd like to just start out with this idea of unmet need. It seems like a lot of the drugs that are coming before us maybe do come with this unmet need and this idea of is it symptoms. It just feels what happens is it does lower -- because of using the fast tracking mechanism, it does lower clinical trial requirements.

So with that being said -- that's just an overall comment. But the first study, 019 -- and I go back to the fact that it was a broad, sweeping

dementia-related psychosis, and that the FDA at that time rejected it, and it wasn't an adequate well-controlled study. It sounds like, from our papers, that the FDA really would have liked to have seen a new study, and that's really what I would have liked to have seen; especially Alzheimer's, when I asked that question earlier, how do we know that they were actually Alzheimer's versus just dementia and were they given brain scans?

So I feel like it becomes very subjective, especially because now we're trying to go, okay, it didn't work here; let's try to go here, and the narrow application, so that I would have liked to have seen, and agreed with the agency, a new study, and yet I know it's expensive, et cetera, to do all of that.

The other issues, that it was over in the UK with predominantly a white population, when we know that here -- and not a whole lot of men as well, but then when we know that, according to the CDC's numbers, predominant Alzheimer's is in the black

population, followed by Latin and white. So that's just something that I know that, overall, a lot of trials have this issue, but I hope that it encourages sponsors and the industry to do a better job on that.

In terms of the 045, then going back to the primary, it didn't reach it. Secondary in my mind is the fact that there wasn't any substantial -- and really, is 2 points meaningful enough to the patient population? And I heard, and I sympathize, when people are talking about what it is like to live in real-world situations with this, but I think it's not set for that.

Then 045, we've got the different subgroups, and I think whether it's Parkinson's, or the Lewy bodies, or Alzheimer's, it just feels like it was too all put together, and it's hard to parcel out; that, again, from what I have understood in my layperson is that a lot of times Parkinson's, could that be the psychosis because the drugs that are used to treat as opposed to Alzheimer's, which is a different type of psychosis or mechanism that does

creates that.

Then in terms of the last study using the original Parkinson's psychosis, I think it's far-reaching. It doesn't feel relevant. It feels like we're just reaching for straws so that we can get this unmet need, and we can get out there and market. I don't know who is right before me, but she mentioned something of aren't there -- I mean, I would assume, since I've heard many times at this committee that the FDA is not in the business of regulating off label, that I would think there are probably physicians out there right now that have been using this drug off label, so I just say that.

Then, of course, I'm not even touching safety yet because I know that's not what we're doing. But safety is always a concern, and given even just the last Parkinson's psychosis, we know what's happening in the latest rounds of data on the safety that's coming out of that, and Alzheimer's is a longer term disease. So those are some of my concerns with the three studies. Thank you.

DR. NARENDRAN: This is Raj Narendran. I'm just going to add in that I agree that it kind of met the primary endpoint, Study 019, but I feel like there were too many issues in terms of the scales used were not well quantified, or it was a very severely cognitively compromised population where symptoms fluctuate a lot, so maybe that explains some of the issues there.

The single time point was a concern. I thought the study sample was relatively small because it was designed as a phase 2 study, and the functional outcome issue and lack of response on agitation and aggression, and things that go along with psychosis kind of give me pause to think how effective this drug is, based on Study 019.

Study 045, I felt the randomized-controlled trial design works very well if we know that there is an established data set. Like antipsychotics in schizophrenia, you remove them, and they worsen. It seems fair, or if your efficacy in the short-term trial prospectively is clear-cut defined, based on some mechanism, I think the

randomized-controlled trial design is a good way to look at durability and maintenance, but I don't know if that was the right design to go for. And I think, as we all know, it didn't work out and, unfortunately, was terminated early, and the study was underpowered to gauge its efficacy in Alzheimer's disease psychosis.

The last thing, I do not think the 020 study is relevant here. I think Parkinson's disease psychosis, as we know, is mostly LBD, Lewy body dementia. There's a lot of inclusions. It has a predominance of visual hallucinations. There's a lot more stability for hallucinations in Parkinson's disease as opposed to in Alzheimer's dementia psychosis, it's mostly delusions.

So I'm not sure we can really use that data to support this particular indication. So that was kind of my thoughts.

Is there anybody else who wants to weigh in before I summarize? Did everybody have a chance?

(No response.)

DR. NARENDRAN: I don't see any raised

hands.

(No response.)

DR. NARENDRAN: People forgot to put their hands down.

DR. APOSTOLOVA: Hi. Sorry. It's Liana. I haven't weighed in. It's Liana.

DR. NARENDRAN: Dr. Apostolova?

DR. APOSTOLOVA: It's Liana Apostolova. Yes, thank you.

I guess I'm the one with the more positive outlook from the data that was presented. First of all, I'm a neurologist, a dementia doctor, and I hundred percent care for patients largely with Alzheimer's, and very little with Parkinson's disease dementia, to be honest, with Lewy body dementia. And in my experience, in Alzheimer's per se, unlike in schizophrenia, psychosis doesn't always associate that strongly with agitation and aggression, cognitive decline and the ability of patients to actually understand what's going on; it's more likely to cause aggressive behavior and agitation, and not so much the psychotic episodes.

But that's my observations from the population I care for.

I thought Study 019 met its primary outcome in that the exploratory analysis support the findings after controlling for the protocol deviation. I found the responder analysis by presenting good separation of the curves. My only question was about durability of effect, the various stats [indiscernible] fluctuating after psychosis, unquestionably so.

In terms of Study 045, I found the data on SAPS-H+D and CGI convincing. It is unfortunate that there were not more Alzheimer's disease subjects enrolled for better power, and the study was stopped early. But the effect size in AD meets my expectations. I don't anticipate it to ever match Parkinson's disease dementia or dementia with Lewy body for that matter, and the time to relapse curves were persuasive.

The Parkinson's study in its own doesn't support an indication for Alzheimer's, but the fact that the medication has been on the market and has

been administered to tens of thousands of people safely does matter, as our other options have a black box warning, and have cognitive side effects, and reduce the mobility of our patients by virtue of Parkinsonism.

So there is the unmet need; we tend to ignore that, and also to consider that these advanced dementia trials are very hard to conduct. I cannot help but see more positive than negative in the data presented today. That's it.

DR. NARENDRAN: Thank you.

Is there anybody else on the committee with their hands up?

(No response.)

DR. NARENDRAN: I see everybody's lowered their hands, so I will summarize the discussion I heard so far.

From the committee, we heard mostly from the committee members that the Study 019 was not adequate. People raised the protocol deviations issue, although they felt that somewhat was addressed by the agency's review. There were some

concerns about the separation only at week 6. People felt the effect was very small, and also there were some concerns that it was not maintained.

There were also questions raised about the validity and construct of the outcome measures used, lack of signal in the secondary measures, and lack of functional outcome improvement was a concern People also raised concerns about the ethnic composition. Also I heard that people thought that it was designed as a phase 2 trial, so it didn't provide sufficient evidence as a phase 3 larger trial would have done.

But I also heard some positive comments on 019, that some people felt it was positive and the data was supportive but not perfect. They also felt it was persuasive despite the audit and the deviations. I also heard that it was technically a win.

With respect to Study 045, I heard that the randomized trial by design was not the best to look at the efficacy because of the selection bias of

only including responders and withdrawing the drug. People also felt that the premature termination of the study, because it was underpowered to really gauge the efficacy in Alzheimer's disease psychosis, was unfortunate that it was terminated early. I also heard that the dopaminergic drug issue is not very convincing, and I also heard that the post hoc analysis in the separate groups is not necessarily a randomized comparison to provide us clear-cut efficacy data.

With respect to the Parkinson's disease psychosis 020 study relevant to here, I felt many people say it was not relevant or the relevance was unclear. People thought there was a different illness, but people also agreed that there was some overlap between the two conditions, and maybe there's some biological plausibility that psychosis could be effectively treated with pimavanserin.

I also heard that because it has been administered safely for a large population, PDP population, it could be reasonable to go forward.

That's my summary. We would like to move to

question number 2.

Is there anything else anybody wants to add to the summary before I move to the voting question?

(No response.)

DR. NARENDRAN: I do not see any other hands raised. If there is no further discussion on the discussion question, we will now move to the next question, which is a voting question. Dr. Joyce Frimpong will provide the instructions for the voting.

DR. FRIMPONG: Question 2 is a voting question. Voting members will use the Adobe Connect platform to submit their votes for this meeting. After the chairperson has read the voting question into the record, and all questions and discussions regarding the wording of the vote question are complete, the chairperson will announce that voting will begin.

If you are a voting member, you'll be moved to a breakout room. A new display will appear where you can submit your vote. There will be no

discussion in the breakout room. You should select the radio button that is the round circular button in the window that corresponds to your vote, yes, no, or abstain. You should not leave the "no vote" choice selected. Please note, you do not need to submit or send your vote. Again, you only need to select the radio button that corresponds to your vote.

You'll have the opportunity to change your vote until the vote is announced as closed. Once all voting members have selected their vote, I will announce that the vote is closed. Next, the vote results will be displayed on the screen. I will read the vote results from the screen into the record.

Thereafter, the chairperson will go down the roster, and each voting member will state their name and their vote into the record. You can also state the reason why you voted as you did, if you want to, however, you should also address any subparts of the voting question, if any.

Are there any questions about the voting

process before we begin?

DR. STANDER: Yes. This is Dr. Stander; just a quick question. It says for the no vote, if you vote that way, of if not, if it's yes, you're supposed to provide your rationale. Is there going to be someplace to type that in on the site?

DR. FRIMPONG: No, for your rationale, when you vote, Dr. Narendran will ask you your reason why you voted as you did, and you can state.

DR. STANDER: Okay. Thank you.

DR. FRIMPONG: No problem.

Alright, Dr. Narendran.

DR. NARENDRAN: Okay.

So our voting question, question number 2, does the available evidence support the conclusion that pimavanserin is effective for the treatment of hallucinations and delusions in the Alzheimer's disease psychosis population? If yes, provide the rationale. If no, provide the rationale and a recommendation for what further evidence should be generated.

Are there any questions about the question

concerning the wording before we decide to vote? If you do have questions about the wording, please raise your hand.

(No response.)

DR. NARENDRAN: It seems pretty clear.

Joyce, I'll hand it to you.

DR. FRIMPONG: We will now move voting members to the voting breakout room to vote only. There will be no discussion in the voting breakout room.

(Voting.)

DR. FRIMPONG: The voting has closed and is now complete. Once the vote results display, I will read the vote result into the record.

(Pause.)

DR. FRIMPONG: The vote results are displayed. I will read the vote totals into the record. The chairperson will go down the list and each voting member will state their name and their vote into the record. You can also state the reason why you voted as you did, if you want to, however, you should also address any subparts of

the voting questions, if any.

For our result, we have 3 yeses, 9 noes, and no abstained.

DR. NARENDRAN: Thank you.

We will now go down the list and have everyone who voted state their name and vote into the record. You may also want to address the subpart questions and provide the rationale if you voted yes, and if no, provide the rationale and a recommendation for what further evidence should be generated.

We will start with Dr. Johnston.

MS. JOHNSTON: Thank you. That would be giving me a promotion. I'm actually the patient advocate.

DR. NARENDRAN: Ms. Johnston. Sorry.

MS. JOHNSTON: I did vote yes, and my name is Colette Johnston. What I thought was going to be a fairly easy day turned out to be very difficult for me. I have over 25 years of experience in reviewing clinical trials on various IRBs, and from that perspective, I have so many

concerns, and they're all the concerns that have been addressed, from patient population, to informed consent, to this not being applicable to our patient population.

That said, my role here today is as a patient advocate, so I have to take myself back to the night I got a phone call that my father in a care center had just been in a physical altercation with another patient, and who was the most docile, kind man you would ever meet. And I'm 250 miles away, and the only thing they can do is send him to a psych ward in an ambulance.

If I would have had the opportunity to use this drug, that whole scenario would have changed, and the next two months of his life before he passed could not have been -- possibly would not have been -- spent in a drug-induced sedation.

So from a patient advocate's point, I know that desperation should not drive us, and I do feel like this is being pushed towards the market, and I have to say I was fairly safe in my yes vote because it was pretty obvious that we were going to

have more noes. I couldn't look at somebody in that position and justify that they couldn't have access to that drug, especially since it's being used off label. So that's my rationale.

DR. NARENDRAN: Sorry. I lost connection.

Dr. Follmann?

DR. FOLLMANN: Yes. Thanks. This is Dean Follmann of NIAID. I voted no, and I think the reasons I articulated in the last question, and I agree with a lot of what had been said.

In terms of further evidence, I'd like to see a randomized trial in ADP. And just one small comment on that, I've not really seen the randomized withdrawal design before, but it seems like if you have such a design and you show a striking benefit, then you would want to give those randomized to placebo the effective drug. And you could do this in a blinded way and look at what is the change; like a symptoms score at the time they get the drug, or in a blinded way, the drug people continue to get the drug, look at the change.

If something like that had been done in 045,

we would have additional evidence; yes, we'd have evidence whether the drug worked or not; so anyway, just a consideration for a future twist on a randomized withdrawal design. That's all.

DR. NARENDRAN: Dr. Fiedorowicz?

DR. FIEDOROWICZ: Yes. Jess Fiedorowicz. My vote was a no. A lot of the reasons were clear from the prior discussion. As far as further evidence, I would suggest a phase 3, an RCT in Alzheimer's psychosis, as was proposed by that original Lancet paper for Study 019.

I do want to also just add that while I understood from the applicant and the agency that the original protocol specified 6 weeks, the registration is what is available to the global public and the scientific community, and I do want to underscore that. For any such follow-up study, I think everyone's already touched on this, but the adequate representation, particularly racial representation, of this study would be valuable. Thank you.

DR. NARENDRAN: Ms. Witczak?

MS. WITCZAK: Kim Witczak, Woodymatters, consumer rep. I voted no, and I articulated a lot of the reasons in prior conversation. But again, I always say that without the benefit, we also must look at the harms in totality, although I know that wasn't our assignment.

Then in terms of what I would like to see, and we heard it from Colette, and from people, and the public speakers, that there is a desire and a need for this, but I would encourage the sponsor to do a phase 3 in the proper population with the proper racial ethnic background, as well as test for Alzheimer's disease. And I would love to see those results and see what comes back with it.

So that would be my encouragement, and again, thank you for today.

DR. NARENDRAN: Thank you.

Dr. Apostolova?

DR. APOSTOLOVA: Hi. Liana Apostolova, Indiana University. I voted yes, and the rationale behind that is that despite the fact that both studies were small in terms of AD population, there

was modest efficacy in both, which survived after controlling for protocol deviations, and it also was evident in the prematurely stopped trial, to some extent.

I also am swayed by the fact that there is real-life use data on pimavanserin, and we know it's safe. It doesn't cause the side effects like typical antipsychotics, which is the only other class of drugs we have available, so my vote is yes. Thank you.

DR. NARENDRAN: Thank you.

Dr. Thambisetty?

DR. THAMBISETTY: Thank you, Dr. Narendran. Madhav Thambisetty, NIH. I voted no, and I think all of the reasons for my vote were described in the discussion question, number 1.

As far as what further evidence should be generated, I would echo back what the FDA advised the applicant in the June 2021 Type A review meeting, as well as the December 2021 Type B guidance meeting, when they advised that an additional adequate and well-controlled study in AD

psychosis would likely provide the strongest data and support of a resubmission. So I would echo that advice. I think they got it spot on.

If I may just add on an unrelated note, I found the patient testimony today extremely moving and powerful. I myself am a neurologist who has cared for patients for more than 20 years. I recognize the unmet need in the field. I just think that the unmet need should not be a justification for us to cut corners. It should, on the other hand, inspire us to do the best science and apply the most rigorous standard to analyzing the results from those studies.

In this context, I would also like to acknowledge the significant contributions that the applicant has made. I think these are incredibly difficult studies to run in very, very difficult patients, and I think the applicant also might be congratulated for doing their best to bring tangible benefits to our patients. Thank you very much.

DR. NARENDRAN: Thank you.

Dr. Cudkowicz?

DR. CUDKOWICZ: Yes. Merit Cudkowicz. I voted yes, and the reason was that Study 019 was positive. It was a primary outcome that was agreed on in advance with the FDA, and is not atypical for looking at psychiatric symptoms. I think 6 weeks and getting their faster is highly relevant for people suffering from psychosis and Alzheimer's and for their family members.

I thought 045 was mildly supportive, no new safety issues, and I was persuaded by the disease experts' points about the similarities and the biology of hallucinations and delusions in Parkinson's and Alzheimer's.

I do think that there are open questions still, but that many of those could be addressed in a postmarketing type study. Thank you.

DR. NARENDRAN: Thank you.

Dr. Stander?

DR. STANDER: Yes. Thank you. I voted no. I expressed many of my concerns, which are similar to those expressed by others just relatively

limited at the [indiscernible] and in a limited population. As Dr. Thambisetty said, I think it's very commendable the applicant is trying to conduct very difficult studies. And as I said earlier, I can empathize and identify with those in the community and elsewhere who acknowledged and expressed their deep concern in the need for effective therapies in this domain, but I do have also concerns that once medications or treatments are made available for problems like this, it's a little like the genie being let out of the bottle, and they tend to get used for a wide range of symptoms for patients that may not really be applicable, extreme costs, and show negative effects.

So I would recommend, as others have said, a more fine study focused entirely on the Alzheimer's population, and preferably from my perspective, longer duration of efficacy that is showing benefit for 6 weeks or [indiscernible]. Thank you.

DR. NARENDRAN: Thank you.

Raj Narendran, and I voted no for the

reasons mentioned before. I think an additional randomized-controlled trial which maybe incorporates some Alzheimer's blood markers, which is a bigger sample size with better outcome measures I think would be reasonable to generate strong data to support an indication going forward. That's all I have to say.

Dr. Iyengar, you're next.

DR. IYENGAR: This is Satish Iyengar from Pittsburgh. I also voted no for the reasons I stated before. I also think that what's really needed is a well-powered study on a demographically appropriate and large ADP sample. Thank you.

DR. NARENDRAN: Dr. Krishna

DR. KRISHNA: This is Sonia Krishna. I voted no for the discussion we've had, and I would like to add that, yes, I also would agree with a new study just in this patient population. And I'm also very interested to find out what has been going on for the past six years when this drug has been out, and other people have used it, even anecdotal information maybe from the community

providers who have been treating these patients. Thank you.

DR. NARENDRAN: Thank you.

Dr. Dunn?

DR. W. DUNN: Walter Dunn, UCLA. I voted no based on the interpretation that the term "conclusion" in the question requires compelling evidence. I do think that Study 019 provides some evidence that pimavanserin can be effective in Alzheimer's dementia psychosis, but that further study is warranted to reach a level of a conclusion.

But I would give Study 019 partial credit; again, technically a positive study, but attenuated by, one, the positive outcome in week 6 looks like it's being driven by worsening in the placebo arm, which appears unrelated to the disease process; two, limitations in the primary outcome scale captured only a narrow view of symptoms and impairment; and then three, lack of concurrence of course in the secondary outcomes.

As far as Study 045, the only two

conclusions I can make is that there is a differential response between Parkinson's and Alzheimer's disease psychosis, and that pimavanserin can be very effective as a maintenance treatment for Parkinson's disease psychosis. Accordingly, therefore Study 020 in Parkinson's patients would not support efficacy in the Alzheimer's population.

In terms of what additional evidence should be generated, I think there is no way around the need to run another study, specifically in the Alzheimer's population. However, if the division is agreeable, I believe a positive randomized withdrawal study would provide compelling evidence. I think that's despite what's been said about such designs enriching for responsive patients.

All that being said, I'd like to return back to my original thought about narrow versus broad considerations. The questions before the committee have been narrow and precise, so I trust that the agency will take a broad approach in their final decision about approval. There are many factors

which we have not formally discussed today such as safety and unmet clinical need. There's clearly a need in this highly vulnerable population. As a clinician, I am a proponent for having as many tools in the toolbox as possible, so I trust the agency will take into consideration all these factors in their final decision.

I would also like to convey the final message to the sponsor and payors if advocating for our patients about improving access to this drug. As this is an approved medication already on the market, the real issue at hand with this approval is about lowering the financial barriers to access this treatment. Therefore, improving access is something well within the capability of the company and payors without having to involve the agency. Thank you.

DR. NARENDRAN: Thank you.

So it seems like from what I heard, just to summarize, many of the members wanted to see an additional controlled randomized trial. Some people thought a positive randomized withdrawal

trial would suffice. People wanted to see adequate representation in terms of ethnicity and race. Also, people wanted to see a trial where there's a longer duration of efficacy being assessed.

The people who voted yes felt there was a strong unmet need. They felt there was modest efficacy and a reasonable signal, although small, within the two trials that were done, especially 019, which many members who even voted no had agreed that it met the positive endpoint.

Other people who voted yes felt that the drug is already available and doesn't have any safety concerns as available atypical antipsychotics which are used to treat patients off-label. So that's my summary.

Are there any other comments from the agency before we adjourn the meeting? Anybody from the agency want to comment or make any last --

(No response.)

DR. NARENDRAN: Dr. Farchione, if you're there?

DR. BOSSIE: Hi. This is Paul -- I'm sorry.

Go ahead, Bernie.

DR. FISCHER: Hi. This is Bernie, deputy for psychiatry. Tiffany just had her call drop, an inopportune moment. But I just wanted to thank the members of the AC for their careful consideration, thank the public hearing comments, and we will take all of this under consideration when making our decision.

Adjournment

DR. NARENDRAN: Thank you, Dr. Fischer.

We will now adjourn the meeting. Thank you, everyone, for attending. I do want to thank the sponsor. I want to thank all the people who participated in the open public hearing and gave powerful testimony, and I also want to thank the agency staff for all the hard work they do. Thank you.

(Whereupon, at 4:21 p.m., the meeting was adjourned.)