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JOINT MEETING OF THE PSYCHOPHARMACOLOGIC DRUGS ADVISORY COMMITTEE (PDAC) AND THE PERIPHERAL AND CENTRAL NERVOUS SYSTEM ADVISORY COMMITTEE (PCNS)

Virtual Meeting

Friday, April 14, 2023

9:00 a.m. to 3:26 p.m.

Meeting Roster

DESIGNATED FEDERAL OFFICER (Non-Voting)

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

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Department of Statistics
University of Pittsburgh
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Rajesh Narendran, MD

(Chairperson)

Attending Psychiatrist

resolve Crisis Services

UPMC Western Psychiatric Hospital

Professor in Radiology and Psychiatry

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Patrick S. Thomas, Jr., MD, PhD

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Baylor College of Medicine, Menninger Clinic

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Kim O. Witczak

(Consumer Representative)

Co-Founder, Executive Director

Woodymatters

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PSYCHOPHARMACOLOGIC DRUGS ADVISORY COMMITTEE MEMBER

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Robert W. Baker, MD

(Industry Representative)

Deputy Chief Medical Officer and

Senior Vice President (retired)

Eli Lilly and Company

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Julieanne Dorn Professor of Neurology

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Liana G. Apostolova, MD, MSc, FAAN

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Barbara and Peer Baekgaard Chair in Alzheimer's Disease Research

Professor in Radiology and Medical and Molecular Genetics

Indiana University School of Medicine

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David Weisman, MD

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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

(9:00 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. My name is Raj Narendran, and I will be chairing this meeting. I will now call April 14, 2023 joint meeting of the Psychopharmacologic Drugs Advisory Committee and the Peripheral and Central Nervous System Drugs Advisory Committee meeting to order. Dr. Joy 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. Jess Fiedorowicz?

DR. FIEDOROWICZ: Hello. I'm Jess Fiedorowicz, and I'm with the University of Ottawa.

DR. FRIMPONG: Dr. Satish Iyengar?

DR. IYENGAR: Hello. My name is Satish Iyengar. I am in the statistics department at the University of Pittsburgh.

DR. FRIMPONG: Dr. Rajesh Narendran?

DR. NARENDRAN: I'm Raj Narendran. I'm a psychiatrist at the University of Pittsburgh, UPMC health system.

DR. FRIMPONG: Dr. Patrick Thomas?

DR. THOMAS: Hello. My name is Patrick Thomas. I'm a psychiatrist at Baylor College of Medicine.

DR. FRIMPONG: Ms. Kim Witczak?

MS. WITCZAK: Good morning. Kim Witczak, consumer representative with Woodymatters, a drug safety organization in Minneapolis, Minnesota.

DR. FRIMPONG: Dr. Robert Baker?

DR. BAKER: Good morning, Dr. Frimpong. Hi. This is Robert Baker. I've happily, since the start of this year, been retired, but I was at Eli Lilly, where I worked in drug development and drug safety, and before that I was a psychiatrist, University of

Mississippi, University of Pittsburgh.

DR. FRIMPONG: Dr. Merit Cudkowicz?

DR. CUDKOWICZ: I'm a neurologist at Mass General Hospital, Harvard Medical School.

DR. FRIMPONG: Dr. Liana Apostolova?

DR. APOSTOLOVA: Good morning. I'm Liana Apostolova, and I'm a neurologist at Indiana University.

DR. FRIMPONG: Ms. Colette Johnston?

MS. JOHNSTON: Good morning. I'm Colette Johnston. I'm the patient advocate.

DR. FRIMPONG: Dr. Sabrina Paganoni?

DR. PAGANONI: Hello. I'm Sabrina Paganoni. I'm a physician investigator and Mass General, Brigham, and Harvard Medical School.

DR. FRIMPONG: Dr. David Weisman?

DR. WEISMAN: Hi. I'm Dave Weisman, and I'm a neurologist in practice around Philadelphia at Abington Neuro.

DR. FRIMPONG: And now for our FDA participants, Dr. Teresa Buracchio?

DR. BURACCHIO: Hello. I'm Dr. Teresa

Buracchio. I am the acting office director for the Office of Neuroscience.

DR. FRIMPONG: Dr. Tiffany Farchione?

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

DR. FRIMPONG: Dr. Bernard Fischer?

DR. FISCHER: Good morning. I'm Bernie Fischer. I'm the deputy director for psychiatry in the Office of New Drugs.

DR. FRIMPONG: Dr. Marc Stone?

DR. STONE: Yes. I am Marc Stone. I'm the deputy director for safety in the Division of Psychiatry.

DR. FRIMPONG: Dr. Jean Kim?

DR. KIM: Hi. I'm Dr. Jean Kim, clinical team lead in the Division of Psychiatry.

DR. FRIMPONG: Dr. Shamir Kalaria?

DR. KALARIA: Good morning. I'm Shamir Kalaria. I'm a clinical reviewer within the Division of Psychiatry.

DR. FRIMPONG: Dr. Peiling Yang?

DR. P. YANG: Hi. I'm Peiling Yang. I'm a

biometrics team leader in the Office of Biostatistics.

DR. FRIMPONG: And Dr. Kelly Yang?

DR. K. YANG: Hi. I'm Kelly Yang, biometrics reviewer in the Office of Biometrics. Thank you.

DR. FRIMPONG: That concludes the meeting roster.

Dr. Narendran, now to you.

DR. NARENDRAN: Thank you, Joyce.

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 the 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 they're 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 joint meeting of the Psychopharmacologic Drugs Advisory Committee and the Peripheral and Central Nervous System Drug 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

committees 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 these committees 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 that 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 the discussions of today's meeting, members and temporary voting members of these committees have been screened for potential financial conflicts of interests 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 supplement new drug application 205422 s009, efficacy supplement for Rexulti, brexpiprazole, tablets, submitted by Otsuka Pharmaceutical Company, Limited and Lundbeck, Incorporated, for the proposed treatment of agitation associated with Alzheimer's dementia. This is a particular matters meeting during which specific matters related to Otsuka Pharmaceutical's and Lundbeck's supplemental new

drug application 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)(3) to Dr. David Weisman. Dr. Weisman's waiver includes his employer's research funded by John Hopkins Bloomberg School of Public Health Center for Clinical Trials and National Institute on Aging for which his employer receives between $5,000 to 15,000 per year, and Dr. Weisman receives between $0 to $5,000 per year in salary support.

The waiver allows this individual to participate fully in today's deliberations. FDA's reasons for issuing the waiver are described in the waiver documents, which are posted on FDA's website. Copies 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 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 a regulated industry. Dr. Baker's role at this meeting is to represent industry in general and not any particular company.

We would like to remind members and temporary voting members that if the discussion involves 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 participants to advise the committees of any financial relationships that they may have with the firm at issue. Thank you.

DR. NARENDRAN: We will now proceed with the FDA's introductory remarks from Dr. Tiffany Farchione.

FDA Opening Remarks - Tiffany Farchione

DR. FARCHIONE: Hi. Good morning everyone. As noted, my name is Tiffany Farchione. I'm the director of the Division of Psychiatry here at FDA, and today we're going to be discussing the application for brexpiprazole, for the treatment of agitation associated with Alzheimer's dementia.

As everyone on this committee likely knows, Alzheimer's disease is the most common cause of dementia, with an estimated U.S. prevalence of around 6.5 million people over age 65, and although cognitive decline is the predominant symptom, behavioral and psychological symptoms of dementia, or BPSD, including agitation, aggression, irritability, are very common. BPSD symptoms are associated with a higher risk of accelerated disease progression, functional decline, decreased quality of life, greater caregiver burden, increased out-of-home placement, and earlier death.

The clinical presentation and frequency of BPSD symptoms can vary, but most patients experience an initial onset of symptoms in the later stages of Alzheimer's disease and worsening symptoms as Alzheimer's progresses.

So today we're going to talk specifically about agitation associated with Alzheimer's disease. Agitation is among the most persistent and challenging aspects of care among patients with BPSD. The estimated prevalence of agitation associated with Alzheimer's is approximately 40 percent, with higher rates observed in patients living in long-term care facilities relative to those living in the community.

In 2015, the International Psychogeriatric Association formed the Agitation Definition Working Group to establish a consensus definition of agitation and cognitive disorders. This definition was finalized and updated just last year. The definition includes four criteria that must be met: one, the presence of cognitive impairment or dementia; the types and duration of behaviors to be considered; that the symptoms have to be associated

with excess distress or produce excess disability; and the symptoms must not be attributable to some other condition.

At the moment, there is an unmet medical need for this condition. The clinical management of agitation is a challenge. Currently, non-pharmacological approaches include cognitive stimulation, group therapy, exercise, music therapy, multisensory therapy, but there's no FDA-approved pharmacological options. Nonetheless, off-label treatment is common and can include benzodiazepines, antihistamines, antidepressants, antiepileptics, and, of course, antipsychotics. But studies evaluating off-label pharmacological treatments are very heterogeneous in design and in their patient populations, and the results have only demonstrated small improvements related to efficacy, but with serious risks and with tolerability concerns.

Specifically focusing on the use of antipsychotics for the treatment of agitation, they are typically used as a first-line treatment, and the American Psychiatric Association practice guidelines

actually recommend the use of non-emergency antipsychotic medications for the treatment of agitation in patients with dementia. But in 2005, we actually added a boxed warning to all of the antipsychotic label for the increased risk of mortality in elderly patients with dementia-related psychosis who were receiving antipsychotic treatment, and it was about a 70 percent increase.

After the boxed warning was implemented, various regulatory bodies and healthcare institutions have taken additional action to try to limit the off-label use of antipsychotics, but drug utilization data actually indicate that although there have been an overall decrease in antipsychotic use, there has also been an increase in the use of other medications, like opioids, antiepileptics benzodiazepines, among elderly patients with dementia.

There is limited evidence to support the alternative to antipsychotics. That leaves healthcare providers with unclear choices for treatment, and although there's no FDA-approved

treatments for agitation, antipsychotics are still commonly prescribed off-label despite the limited benefits observed in studies that have been conducted thus far and that are described in the literature, and also the increased risk of mortality.

So today we actually have an application in house for an antipsychotic that is intended to treat agitation associated with Alzheimer's dementia. We just have one voting question for the committee today, but we really want to focus quite a bit on the discussion aspect of this application.

We want the committee to discuss the overall benefit-risk assessment of brexpiprazole for the treatment of agitation associated with Alzheimer's disease, and we want that discussion to take into consideration the increase risk of death among elderly patients with dementia receiving antipsychotics, as well as the risk of medications that are often used off-label for the treatment of agitation without established evidence of efficacy.

We also want the committee to discuss whether there's a population of patients with Alzheimer's for

whom the benefit-risk appears acceptable and is there a population for whom the benefit-risk doesn't appear favorable; so really both sides of that equation. And finally, for the voting question today, has the applicant provided sufficient data to allow identification of a population in whom the benefits of treating agitation associated with Alzheimer's with brexpiprazole outweigh the risks? If you don't believe that they've provided that data, what additional data would be needed to support the use of brexpiprazole for the treatment of agitation associated with Alzheimer's?

So that's the charge to the committee today, and with that, I will hand it back to Dr. Narendran.

DR. NARENDRAN: Thank you.

Both the Food and Drug Administration 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 applicant, such as consulting fees, travel expenses, honoraria, and interest in the applicant, including equity interests and those based upon the outcome of the 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 Otsuka Pharmaceutical Company, Limited's presentation.

Applicant Presentation - Mary Hobart

DR. HOBART: Good morning. I'm Mary Hobart, vice president for Global Regulatory Affairs at Otsuka Pharmaceutical. I want to thank the chair, members of the committee, the FDA, and members of the

public watching today. I'd also like to thank the patients and their families who participated in our clinical trials. They, more than anyone, know how difficult and destructive agitation associated with Alzheimer's dementia, or AAD, can be. For many, AAD is accompanied with poor health outcomes, increased institutionalization, and caregiver distress, and, unfortunately, there are no approved therapies to treat this devastating disease.

We are here today to discuss a supplemental indication for brexpiprazole when dosed 2-to-3 milligrams daily, for the treatment of agitation associated with Alzheimer's dementia or AAD. We want to be clear. We are not proposing to remove the boxed warning and look forward to discussing final labeling with the agency. Let me provide some brief background on the regulatory history of brexpiprazole.

Brexpiprazole, or Rexulti, was approved in the U.S. in 2015 for the treatment of schizophrenia and for use as adjunct treatment to antidepressants for the treatment of major depressive disorder.

Brexpiprazole is also approved for schizophrenia and, where applicable, MDD in more than 60 countries, including the European Union and Canada. Through May of 2022, the data cutoff date for this supplemental marketing application, we estimate that there are over 1 million patient-years experience with brexpiprazole from clinical studies and postmarketing experience.

With that background, let me review the clinical program and key regulatory interactions related to our supplemental NDA. Two phase 3 studies, Trial 283 and Trial 284, were conducted concurrently. Key trial design elements, such as the patient population, dosing, and endpoints, were agreed upon with the FDA at a 2012 pre-IND meeting. In 2015, brexpiprazole was granted fast-track designation by the FDA. In 2018, we met with the FDA to agree upon the design and enrichment criteria for a third phase 3 study, Trial 213, which included both higher doses of 2-and-3 milligrams brexpiprazole and an enriched population.

To address the FDA's request for long-term

safety data, patients who completed Study 213 were allowed to enroll in our open-label trial, 182, where all patients were treated with brexpiprazole. This provided an additional 3 months of treatment for a total of 6 months of treatment. The supplemental NDA was submitted to the FDA in 2022 and was accepted for priority review.

Today we will discuss the results from these three global, randomized, placebo-controlled, phase 3 trials that support the efficacy and safety of brexpiprazole. Results from the two fixed-dose trials, 283 and 213, demonstrated the superiority of brexpiprazole 2-and-3 milligrams a day compared with placebo in reducing symptoms of agitation. These results are supported by the flexible-dose study, 284. Overall, these data demonstrate a positive benefit-risk for brexpiprazole in the treatment of agitation associated with Alzheimer's dementia when dosed 2-to-3 milligrams once daily.

The results of the phase 3 program show that brexpiprazole provides statistically significant and clinically meaningful improvements in key measures of

agitation when compared with placebo. The tolerability profile was favorable, particularly when compared with off-label therapies, and adverse events were consistent with those previously reported with brexpiprazole and generally observed in this patient population. Overall, this evidence indicates that brexpiprazole treatment could address a critical unmet need and provide substantial improvement relative to currently utilized off-label treatment options.

Here is our agenda for the rest of the presentation. Dr. Ismail will present unmet need; followed by Dr. McQuade to share efficacy; and Dr. Kraus will review the safety. Dr. Atri will finally provide his clinical perspective, and then I will return to summarize the benefit-risk of brexpiprazole and address your questions.

We also have some additional responders with us today to help with questions. All outside experts have been compensated for their time and travel to today's meeting. Thank you, and I will now turn the presentation to Dr. Ismail.

Applicant Presentation - Zahinoor Ismail

DR. ISMAIL: Thank you, and good morning. I'm Zahinoor Ismail, professor of psychiatry, neurology, epidemiology, and pathology at the Hotchkiss Brain Institute in Calgary. I've worked in clinical trials for over 20 years, including multiple antipsychotic trials, as well as AD trials. I've been the site PI for several agitation in Alzheimer's trials. I see agitation in the outpatient cognitive neurology clinic and in seniors' homes and long-term, which comprise a substantial part of my practice and my research.

I'm here to provide some background on agitation associated with Alzheimer's dementia and the urgent need for treatments for this growing population. Alzheimer's dementia is highly prevalent and expected to increase significantly in coming decades, and as many of you know, Alzheimer's is the most common form of dementia. There are approximately 6.5 million Americans currently living with Alzheimer's dementia, and by 2050, that number is expected to double.

While cognitive impairment is a key feature of Alzheimer's dementia, about half these patients develop agitation. The International Psychogeriatric Association defines agitation in dementia as at least one behavior that causes distress and disability that persists for at least 2 weeks, including behaviors that can be characterized as excessive motor activity like pacing or rocking; verbal aggression such as screaming yelling, shouting, using profanity, arguing or rudeness; or physical aggression like grabbing, shoving, throwing, hitting, banging, destroying property, and physically resisting assistance.

The impact of agitation on this already devastating disease is significant for both the patient and their caregiver. For the patient, agitation is associated with accelerated disease progression, functional decline or quality of life, greater mortality, and institutionalization. For the caregiver, agitation is associated with depression and anxiety and greater burden of care. Caregivers spend over 20 hours per week providing care and assistance, potentially leading to burnout and,

again, patient institutionalization.

Treatment of agitation should follow an evidence-based approach. Treatment guidelines recommend the use of non-pharmacological strategies first; however, this is often infeasible with moderate to severe agitation, so pharmacotherapy is considered despite limited efficacy. Unfortunately, treatment is often initiated only after a clinical emergency, at which point the need is urgent. This delay is generally due to poor recognition of agitation and the lack of indicated treatments, with a consequent reluctance to treat agitation early.

Ultimately, the goal is to reduce agitation and fundamentally to calm without sedation; I repeat, to calm without sedation. As a field, we have conflated and confounded calmness and sedation, but family members see sedation as unnecessary and even punitive. Furthermore, sedation is associated with severe negative clinical outcomes.

I recently saw a patient who came from hospital, where she was treated with risperidone for AAD. She was Parkinsonized [ph] and grossly sedated

such that she didn't interact with her daughter. Both had poor quality of life as a result. Her daughter felt her mother had done a disservice and described her as zombified. Unfortunately, this is not uncommon.

Current pharmacological treatment options require us to balance risks and benefits. Despite the burden of agitation, we still do not have any approved medication for agitation in Alzheimer's dementia in the U.S. As a result, physicians and patients resort to off-label medications such as benzodiazepines, antihistamines, antidepressants, antiepileptics, and antipsychotics. However, these off-label medications show inconsistent, modest effects and carry several notable safety risks, such as sedation, extrapyramidal symptoms, falls, worsened cognitive performance, and cardiovascular and cerebrovascular events. In addition, because these are not approved for AAD, there is not clear labeling to guide their use.

To close, access to a well-documented medication that clearly communicates safety and

efficacy expectations in the product label remains an ongoing and serious unmet need in this patient population. In fact, I think this is amongst the most serious unmet needs. Adequate management of behavioral disturbances is essential to improve the health and safety of patients with agitation in Alzheimer dementia and to ease the burden of care borne by families and other caregivers.

Current care is limited to off-label medications that carry significant risks. Thus, a fundamental need exists for approved medications to treat agitation in Alzheimer's dementia without sedating patients or exacerbating the underlying symptoms; calmness without sedation.

Thank you. I will turn the presentation to Dr. McQuade to review the clinical data.

Applicant Presentation - Robert McQuade

DR. McQUADE: Thank you, Dr. Ismail.

Good morning. I'm Bob McQuade, executive vice president and chief strategic officer at Otsuka. This morning I will review efficacy results from the three phase 3 studies in agitation associated with

Alzheimer's dementia, which support the efficacy of brexpiprazole 2-and-3 milligrams. The program began with two essentially identical clinical studies, Study 283 using fixed doses of 1 or 2 milligrams and Study 284 with flexible dosing between 0.5 and 2 milligrams. These studies support the efficacy of brexpiprazole 2-milligram dose and importantly demonstrate that doses of 1 milligram and lower are not effective.

Based on the results of these studies, and after conversations with FDA, we designed Study 213, whose results confirm the efficacy of both brexpiprazole 2- and 3-milligram doses. Given the chronology and similar design of Studies 283 and 284, I'll describe them together at first.

Studies 283 and 284 were designed based on feedback from the FDA at a pre-IND meeting and were conducted concurrently. Both were 12-week, double-blind, placebo-controlled studies. In fixed-dose Study 283, patients were randomized and titrated over a 4-week period to target doses of 2 milligrams, or 1-milligram brexpiprazole, or

placebo. Study 284 was a flexible-dose study in which patients received either titrated doses of brexpiprazole or placebo. In this study, investigators could decide after 4 weeks to keep the patient at 1-milligram brexpiprazole or increase the dose to 2 milligrams.

Each study had a 30-day safety follow-up assessment. It is important to note that Study 283 was also initiated with a dose group targeting 0.5 milligrams, but that group was terminated early in the conduct of the study, and only 20 patients were randomized to this group. We will not be discussing the efficacy of this group in the remainder of this presentation, but the patients are included in the safety evaluation.

The primary endpoint for both studies was the mean change from baseline to week 12 in the Cohen-Mansfield Agitation Inventory or CMAI Total Score. The selection was agreed to at the pre-IND meeting in 2012. The key secondary endpoint was the mean change from baseline to week 12 on the Clinical Global Impression of Severity, or CGI-S score,

specifically as related to agitation.

The Cohen-Mansfield Agitation Inventory, or CMAI, is a well-established questionnaire that measures the frequency of 29 manifestations of agitated behaviors in elderly persons. It has been judged to be appropriate for this population and has become the scale of choice in Assessing agitation in clinical studies.

Based on factor analysis by Rabinowitz, et al., the agitation symptoms have been clustered into three key factors: namely, aggressive behavior, physical non-aggressive behavior, and verbal agitated behavior. Each behavior is rated on a 7-point scale of frequency, with higher ratings corresponding to higher frequency of the agitated behavior. The ratings pertain to the 2 weeks preceding administration of the CMAI. The observations are communicated by the caregiver and scored by a qualified and certified clinician. It is important to note that a score of 1 on any behavior represents absence of that behavior; thus, the lowest score possible, which represents the absence of all

agitated behaviors, is 29, and the highest possible score is 203, which would be equivalent to every symptom occurring several times an hour.

The CMAI is a behavioral inventory where reductions from higher initial scores may be more meaningful than reductions from lower initial scores. For example, a 2-point drop from a baseline score of 6 means a behavior occurring several times a day has improved to several times a week. Conversely, a 2-point drop from a baseline score of 3 means a behavior occurring once or twice a week improves to not occurring at all.

Turning to key enrollment criteria, the studies enrolled patients 55-to-90 years of age who had a diagnosis of Alzheimer's disease. At screening and baseline visits, participants had to have a Mini-Mental State Examination score of 5 to 22 and a total score of at least 4 on the agitation aggression item of the Neuropsychiatric Inventory. Patients were excluded if they had dementia or memory impairment not due to Alzheimer's dementia: a history of stroke or pulmonary or cerebral embolism;

delirium; or exhibited a serious risk of suicide.

Key demographic characteristics were similar and generally balanced across the two studies and the brexpiprazole and placebo groups for each study. The mean age was 74, and the majority of participants were female and white. Across the two studies, approximately 3-to-4 percent of patients were black or African American, but black or African American patients constituted about 10-to-15 percent of the U.S. study population, which is consistent with the proportion of blacks and African Americans with Alzheimer's disease in the U.S.

Both studies were representative of patients with agitation associated with Alzheimer's dementia, and both enrolled patients with similar baseline disease characteristics. CMAI total scores ranged from 68.5 to 72, and CGI severity scores for agitation were an average of 4.5 across arms, which represented moderate to markedly severe agitation. Most patients' Alzheimer's dementia was classified as moderate to severe and with a relatively even distribution of institutionalized versus

community-based patients.

Completion rates in both studies were similar between brexpiprazole and placebo, ranging from 87-to-89 percent. The two most frequently reported reasons for discontinuation were adverse events, about 4-to-6.5 percent of patients, and withdrawal of consent, about 4 percent of patients.

Let's now turn to the primary endpoint results. Study 283 met the primary endpoint and demonstrated that brexpiprazole 2 milligrams daily was statistically superior to placebo, for the mean change in CMAI total score from baseline to week 12, while the 1-milligram dose showed no separation from placebo.

Separation from placebo started to emerge after patients began receiving the 2-milligram dose week 4. On average, patients exhibited a baseline score of 70, and an average 21.6-point improvement from baseline was seen by week 12, representing, a 51 percent improvement from baseline. Separation from placebo was about minus 3.8. Thus, Study 283 strongly supported brexpiprazole 2 milligrams as the

minimum efficacious dose in agitation associated with Alzheimer's dementia.

In Study 284, brexpiprazole 0.5-to-2 milligrams per day group did not achieve statistical significance on the primary endpoint. Improvement from baseline was about minus 18.9, but separation from placebo was only minus 2.3. However, given the dose-dependent results in 283, and the fact that many patients did not achieve the 2-milligram dose in Study 284, we performed a post hoc analysis of the 284 data based on dose.

This post hoc analysis of the subgroup of patients in Study 284, who were uptitrated to brexpiprazole 2 milligrams or to equivalent placebo, demonstrated improvements for the primary endpoint compared with placebo, with a nominal p-value of 0.012. Again, separation from placebo emerged after patients began receiving the 2-milligram dose. This subgroup represented approximately 57 percent of the overall patients in Study 284. This post hoc analysis further supports brexpiprazole 2 milligrams as a minimum efficacious dose in AAD. I'll now move

on to the key secondary endpoint.

In Study 283, a numerically greater improvement in the mean change in CGIS score as related to agitation, from baseline to week 12, was also observed for the 2-milligram dose, but the treatment difference did not reach statistical significance. Study 284 also showed further improvement compared to placebo, reaching a nominal p-value of 0.016.

Study 283 met its primary endpoint, but Study 284 did not. Thus, the sponsor believed that a second positive pivotal study would be needed for potential approval. Overall, results of Studies 283 and 284 demonstrated efficacy of brex 2 milligrams but not 1 milligram or less, and thereby identified 2 milligrams as the minimally effective dose.

Following review of Studies 283 and 284, we examined factors that might have influenced the efficacy results; in particular as the baseline agitation frequency as represented by the CMAI total score. It was our belief that the MPI score of 4 or greater may have resulted in enrollment of a number

of patients with insufficient agitation at baseline. This was also a hypothesis discussed by the FDA.

As a result, we looked to see whether patients had sufficient baseline agitation. We focused on those symptoms that were more prominent and which were more impactful on patient-caregiver quality of life, including physically and verbally aggressive behaviors. These behaviors constitute the CMAI Factor 1 for aggressive behaviors as shown earlier in this presentation.

Eighty-six percent of patients in both studies met the criteria for Factor 1, and these patients had a higher baseline frequency than those who did not meet the criteria for Factor 1. Patients meeting Factor 1 criteria in Study 283 showed an average baseline CMAI score of about 73, while those who did not meet Factor 1 criteria showed an average baseline score of about 57. Of note, the majority of patients meeting criteria for Factor 1 also showed higher frequency of agitated behaviors belonging to Factors 2 and 3. In addition, the patients that met Factor 1 criteria achieved a greater treatment effect

with brexpiprazole.

To understand the impact of higher baseline agitation, the sponsor and the FDA aligned that patients with more prominent agitated behaviors should be recruited in the future AAD trials to discern change within a 12-week clinical trial. Thus, we define this Factor 1 enriched population to target in our third study.

With this background, let me turn to our third study, Study 213, which incorporates the learnings of the prior two studies. Study 213 was a phase 3, 12-week, double-blind, placebo-controlled, 2-armed, fixed-dose study with a 30-day safety follow-up. Study 213 was similar to Study 283 with a few exceptions.

Based on the prior results, we included the 2-milligram dose as the minimally effective dose, and based on feedback from the FDA, we also include a 3-milligram dose to test a higher dose, as well as a somewhat more rapid titration schedule. The purpose of the 3-milligram dose was to ensure its safety and tolerability profile, as that dose is often used by

clinicians in the treatment of schizophrenia and major depressive disorder. It was also agreed with the agency that we would combine the two doses for our primary and secondary analyses versus placebo.

To ensure enrollment of sufficiently agitated patients, patients enrolled in Study 213 had to meet the same eligibility criteria as the first two trials, with two notable differences, highlighted here in blue, as agreed to by the FDA. Firstly, the diagnosis of agitation needed to meet the IPA provisional definition, which had not been available at the time of the first two studies. Secondly, all patients needed to meet the criteria for Factor 1 at baseline. These changes helped ensure an enriched population with prominent and frequent agitated behaviors at baseline.

The primary and key secondary endpoints were the same as Studies 283 and 284. The demographics were consistent across treatment arms and similar to the prior two studies. The mean age was about 74. Again, the majority of patients were female and white. Roughly 4 percent of patients were black or

African American, which represented about 8 percent of the patients randomized in the U.S.

Disease characteristics in Study 213 were similar to the prior studies, with the exception of the baseline scores for CMAI. As a result of the implemented enrichment criteria, the average CMAI total score was about 80, relative to 70 in the earlier studies, and represented a patient with generally markedly severe symptoms at baseline. Similar to Studies 283 and 284, most patients completed the study, and the main reasons for discontinuation in both treatment groups were adverse events and patient withdrawal of consent at about 5 percent and 4 percent, respectively.

Turning now to endpoint results, Study 213 met the primary endpoint. Treatment with brexpiprazole 2-and-3 milligrams showed statistically significant improvement in the mean change and CMAI total score from baseline to week 12 compared to placebo. Separation between the two groups began at week 6 and increased towards week 12. The improvement in CMAI total score was minus 22.6 and

the effect size versus placebo was minus 5.32 in this study.

The improvement in the CMAI scores were also reflected in the clinician's clinical judgment of severity. Treatment with brexpiprazole 2-and-3 milligrams per day showed statistically significant improvement compared with placebo in the key secondary efficacy endpoint, mean change in CGIS score as related to agitation from baseline to week 12. The difference between treatment groups emerged between week 6 and 8 and exhibited p-values less than 0.01 at weeks 8 through 12.

When we look at the primary endpoint results by dose, we see that both brexpiprazole 2-and-3 milligrams separated from placebo at weeks 8 to 12, and the change from baseline was virtually identical. Clearly, these data indicate that both 2-and-3 milligrams produce clinically meaningful improvement in symptoms of agitation. Furthermore, brexpiprazole-treated patients demonstrated improvements across the three CMAI subscales as defined earlier in the factor structure. This is

important, as it shows that even though the patient population was enriched for aggressive behaviors at baseline, improvements in symptoms were observed across the aggressive, physically non-aggressive, and verbally agitated behaviors with nominal p-values less than 0.05.

We also see a difference in the percentage of patients achieving meaningful reductions in CMAI scores of 20, 30, and 40 percent. Nearly 70 percent of brexpiprazole achieved a 20 percent CMAI response reduction, and more than 20 percent of patients achieved a 40 percent CMAI reduction. The ratio of response rate ranged between 1.41 and 1.62.

There is a strong correlation between improvements in frequency of symptoms and improvements in severity, the CMAI total score and CGIS, respectively. Using methods advised by the FDA, we defined the meaningful within-patient change threshold as a 20-point reduction in the CMAI total score from baseline, which is correlated to a clinically meaningful 2-point improvement in CGIS. When we employ this meaningful within-patient

threshold to Study 213, 56 percent of patients treated with brexpiprazole 2-and-3 milligrams met the threshold as compared to 37 percent of patients receiving placebo. This represents a ratio of response rate of 1.51.

Finally, I want to turn to the data collected in the extension trial that followed the 12-week blinded treatment in Study 213. Patients from Study 213 were enrolled in a 3-month extension trial, Study 182, in which all patients received brexpiprazole. The data from Trial 182 demonstrate continued improvements in CMAI in both the group previously treated with brexpiprazole and the group previously treated with placebo. Both groups of patients exhibited further improvement from baseline, which was defined as their final CMAI score from Study 213.

Larger improvements were observed in patients previously treated with placebo, catching up with the improvements seen in the patients previously treated with brexpiprazole. While fully recognizing that this extension study is open-label and that all

patients are being treated with brexpiprazole, the added benefits observed in patients who have already been treated with placebo for 12 weeks further supports the efficacy of brexpiprazole in this patient population. In addition, patients previously treated with brexpiprazole show continued benefit for up to 24 weeks of treatment.

In summary, brexpiprazole 2-and-3 milligrams demonstrated statistically significant and clinically meaningful improvement in two randomized, placebo-controlled clinical trials for the primary endpoint of change in CMAI total score from baseline to week 12. The bolded text indicates p-values less than 0.05, and the data correlate to a Cohen's d effect size of 0.25 to 0.35.

In addition, Studies 284 and 182 provided supportive data for 2 milligrams being the minimal effective dose, and for benefits out to 24 weeks of treatment, respectively. In totality, the data across all of the studies support consistent benefit on symptoms of agitation in AD. These results support a meaningful benefit in patients with

agitation associated with Alzheimer's dementia and address a significant unmet medical need in the community.

Let me now ask Dr. Kraus to present the safety data.

Applicant Presentation - John Kraus

DR. KRAUS: Thank you, Dr. McQuade.

I'm John Kraus, executive vice president and chief medical officer at Otsuka. Today I'll share the safety data in patients with AAD. Our safety population comes from our three phase 3 studies, 283, 284, and 213. We also have data from our extension study for treatment with brexpiprazole for up to 24 weeks with no new unexpected safety events. Let's start with the overall safety profile.

Overall, the safety profile across all brexpiprazole dose groups was comparable to placebo, demonstrating that in patients with AAD, treatment with brexpiprazole once daily was generally safe and well tolerated, consistent with its established safety profile. The incidence of adverse events was comparable between brexpiprazole fixed dosage groups

and placebo, with half of patients experiencing an adverse event.

AEs leading to discontinuation and serious adverse events were also similar. The deaths in the brexpiprazole 2 milligram, 3 milligram, and placebo groups were one patient each. None of these deaths were considered related to the study drug by the investigator. The most commonly reported adverse events occurring in at least 2 percent of patients were generally consistent with placebo and with the known safety profile of brexpiprazole.

Turning to serious adverse events, overall, serious adverse events were low and comparable to the brexpiprazole 2-to-3 milligrams group and placebo. The nature of these events is consistent with what would be expected in this elderly population. Identified safety topics of special interest included orthostatic hypotension; extrapyramidal symptoms; somnolence; cardiovascular events; cerebrovascular events; and falls. Certain antipsychotics in this patient population are expected to lead to a greater likelihood of experiencing these adverse events.

Overall, these events were generally balanced across the treatment arms. This patient population of advanced age is already at increased risk of underlying cardio and cerebrovascular disease, as well as injuries due to falls, so seeing similar rates of events with placebo in this population is important. There is also no worsening in cognition in these patients with Alzheimer's dementia, as evaluated by the Mini-Mental State Examination, or MMSE, change from baseline compared to placebo.

Turning now to deaths, while there were numerically more deaths in the all brexpiprazole group, it is important to recognize that the mortality rate observed in the brexpiprazole AAD program was low, and is lower than rates reported in meta-analyses for other antipsychotic medications. This includes the FDA meta-analysis, where the mortality rate on treatment was above 4 percent. Other meta-analyses have reported lower rates, but these were still 3-to-4 fold higher than that seen with brexpiprazole.

We do understand that FDA's methodology for

assessing deaths in the brexpiprazole AAD program differed from our predefined analysis plan. Regardless of the methodology, deaths were low across the program. When looking by product, we see that, historically, all other antipsychotics have reported greater mortality rates in their programs as compared to brexpiprazole.

Let me guide you through each of the deaths in the brexpiprazole program, showing that there is no pattern or common etiology in the cause of death. As we are dealing with an elderly population, we need to consider confounding by underlying conditions and other factors that increase the mortality risk, such as advanced age, comorbidities, and concomitant medications consistent with the AAD population. These deaths align with expectations for an elderly population.

Per our safety analysis plan, events leading to deaths were captured during the study period and up to 30 days after study completion. All deaths occurred at least 30 days after beginning study drug administration, suggesting that there were no deaths

associated with acute onset of treatment. We first should consider that brexpiprazole is washed out and fully eliminated from the body in approximately 18-to-19 days, and events occurring beyond 3 weeks are confounded by potential changes in treatment and limitations of data collection. This is why we use 30 days for our safety cutoff. Three of the events occurred more than 3 weeks off therapy, one of which airway obstruction occurred 67 days after stopping brexpiprazole.

To provide some additional context, I will briefly review the deaths related to events occurring within the study period plus 30 days, as listed on this slide. Two deaths occurred on 0.5 milligram treatment; two on 1 milligram treatment, and one each on brexpiprazole 2-and-3 milligrams. There was no pattern in terms of study drug exposure duration or time since last dose prior to death.

All patients had comorbid medical disorders, which included hypertension; atherosclerosis; ischemic heart disease; heart failure; chronic obstructive pulmonary disease; carotid artery

stenosis; and type 2 diabetes, and were thus treated with concomitant medications. The events leading to death are generally consistent with those expected in an elderly population with Alzheimer's disease.

Narratives are included in the briefing document, but to summarize, the brexpiprazole cases included a fall, secondary through the patient's claim of being pushed, with subsequent treatment with clopidogrel, as a myocardial infarction was being ruled out; 22 days after the last dose of study medication, the patient was found unresponsive.

A CT scan revealed left-sided intracranial hemorrhage. The patient died 5 days later, a fatal event of acute purulent meningoencephalitis, which had been preceded by pneumonia and signs of heart failure 2 days after stopping study medication. The patient rapidly. deteriorated from these conditions and died 52 days after first initiating study medication.

Aspiration pneumonia developing 65 days after initiating study medication, which was then stopped, with subsequent fever, agitation, confusion, and

hypoxic respiratory failure. The patient was transferred to hospice care and died 78 days after starting study medication and 13 days after the last dose.

Cardiopulmonary arrest, secondary to airway obstruction, by choking on an orange 25 days after the last dose of study medication. Although resuscitated, the patient remained comatose on mechanical ventilation, ultimately suffering a cardiac arrest and dying 42 days later.

End-stage Alzheimer's dementia with hospice care initiated 5 days after the last dose of medication, and death occurring 9 days after the last dose; and finally, heart failure with death occurring 23 days after the last dose of study medication, which had been preceded by muscle weakness, pneumonia, and cachexia.

There were two additional deaths not included. One patient in Study 284 died 2 days after the 30-day, protocol-specified safety follow-up period from vascular encephalopathy and brain edema, and one patient in Study 284 who died from pancreatic

cancer more than 100 days after the last dose. In no instance did the investigator assess treatment as being related to any of these deaths. Importantly, there were no further deaths among patients who entered the open-label study who were all on brexpiprazole treatment for up to an additional 12 weeks. As you can see, each case is confounded by potentially contributing factors outside of the assigned treatment, yet the overall rate is less than 1 percent.

Turning now to long-term safety, 259 patients who completed the 12-week study period in Study 213 rolled over into the active treatment extension study, 182, and received treatment with brexpiprazole for up to 12 additional weeks. Of these 259 patients, 163 patients receiving brexpiprazole in the double-blind study continued on treatment for a total duration of up to 24 weeks. Brexpiprazole was safe and well tolerated for long-term use up to 24 weeks. There were no unexpected safety events, and as previously stated, no mortalities were observed in the extension period. Overall, the safety profile

was similar to that observed in the double-blind, placebo-controlled studies.

In conclusion, brexpiprazole 2 milligrams and 3 milligrams daily was safe and well tolerated in the extensive safety database among patients with AAD. Adverse events span a wide variety of system organ classes, and the safety profile of brexpiprazole was consistent with that from prior clinical experience among other indications, with high tolerability and low rates of patient discontinuation.

Additionally, there was less than 1 percent of patient deaths on treatment, with no pattern of time after first administration or time since the last dose, no consistent cause of death, and no deaths considered by the investigator as being related to treatment. Overall, brexpiprazole has demonstrated a favorable safety and tolerability profile in patients with agitation in Alzheimer's dementia, consistent with its use in other approved indications.

Thank you. I will now invite Dr. Atri to share his clinical perspective.

Applicant Presentation - Alireza Atri

DR. ATRI: Thank you and good morning. I'm Alireza Atri. It's a pleasure to be with you here today to provide a clinical perspective on the data we've seen. First, I'd like to introduce myself. I'm a cognitive neurologist, and I'm the director of the Banner Sun Health Research Institute in Sun City, Arizona. I also serve as associate director of the NIA P30 funded multi-institutional Arizona Alzheimer's Disease Research Center, where I also direct the clinical core and co-direct the biomarker core of ADRC. As part of my clinical practice, I care for patients and families with Alzheimer's disease and related disorders.

Agitation worsens the impact of an already devastating and burdensome disease, and as described by Dr. Ismail, there's a dire need for approved and safe therapeutic options. I believe that brexpiprazole is a welcomed and much needed option that could provide clinically meaningful benefits for some patients and families, benefits that I believe will translate to better real-world effectiveness

than current off-label treatments due to brexpiprazole's overall favorable benefit-risk profile.

During the course of their illness, particularly more advanced stages, many patients will suffer from severe agitation behaviors that will be refractory to environmental or behavioral interventions or they are severe enough to warrant substantial safety concerns. These agitated behaviors negatively impact the quality of life and the health and well-being of both patients and caregivers. This is what I refer to as the dyads. They negatively impact the patient's ability to receive care and make caregiving even more difficult and burdensome and, unfortunately, our current off-label options are highly problematic with an evidence base that's lacking.

Their limited clinical benefit potential must be balanced against real issues with tolerability and serious side effects, including excessive sedation, falls, Parkinsonism, or increased kinds of impairment. This creates a major damned if you do,

damned if you don't quandary, while sitting on a knife edge, and often leads to what I call a pharmacological and clinical yo-yo and a chasing of our tails. Simply put, we need better options with potential efficacy but that also adhere to the first tenet of medicine, "Above all do no harm."

So let me provide a few examples of this clinical yo-yo that we face every day. These are both two patients that I cared for. They were both in the moderate to severe stages of Alzheimer's disease dementia and were on background treatment with approved AD medications, cholinesterase inhibitors and memantine. We had tried extensive behavioral and environmental approaches in our attempts to mitigate their escalating condition.

One of my patients, he was a 62-year-old gentleman. He was physically healthy, 6 foot 2, 220 pounds, very fit. He had early onset AD and had significant receptive aphasia. He would constantly hum, pace; he had separation anxiety. These were manageable by his wife at the time. She was the sole caregiver. His lifelong personality and demeanor was

described as being a very likable and gentle giant.

He developed these symptoms that initially occurred monthly but ultimately increased to weekly. These were unprovoked episodes of glaring and fury at her. In one instance, he held his 110-pound wife immobile against the wall for about 20 to 30 seconds. At another time, he tried to grab an hold her, but in doing so, ended up actually pushing her over the couch, and she fell.

He was treated with risperidone, but became too sedated and Parkinsonian. His wife couldn't transfer him to the bathroom. We went through this yo-yo where we pulled back and pulled down on the risperidone dose, we had re-emergence of the episodes, then back up again causing excessive Parkinsonism, and ultimately this led to his wife having to prematurely place him in a small group home.

Upon admission, the caregivers at the group home were aware and initially accepting, and could cope with the approximately weekly episodes. But once the frequency increased and involved multiple

caregivers, they became much less tolerant and couldn't cope. They stated that they couldn't manage and insisted that he be kept almost continuously sedated. He went from walking and talking in his home to being sedated and completely bedbound. He became dehydrated, aspirated, and died within a few months.

I also cared for a 56-year-old woman with early onset AD. She had very well preserved language function but substantial visuospatial and praxis difficulties. She was ambulatory, but over months became increasingly resistant to receiving care for hygiene. She would hit family members and caregivers. She would cry and scream every time they approached her to provide this care. She developed skin breakdown and infections, including UTIs. She was given benzodiazepine by a primary care clinician, became too sedated, developed hypernatremia, aspirated, was hospitalized, and given antipsychotics. This led to a fall and a fracture, and she went on to have a stroke.

It is important to remember that the pattern

of symptoms and behaviors are really different for each patient, and not all agitated behaviors will be present in a specific patient, and also that the impact of any behavior will really be different based on the individual characteristics of the dyad. So when I evaluate agitation aggression in my patients, the first thing I assess is what is the acuity and the impact of the overall clinical situation, and what factors could be triggering or exacerbating it, and how could these be amenable to effective interventions in ways that are most practical, and least burdensome, and least risky? Then I dig deeper, and I evaluate the frequency, the severity, the duration, the timing, the triggers, and the impact of the most relevant or distressing behaviors for the given dyad.

The CMAI and the CGI are very structured instruments. They're not often used in clinical practice; however, the overall approach, the process, and the content used in these scales are pretty standard to clinical practices and are often implemented in a more holistic way and a less

structured way by clinicians. I use a process similar to the CGI to first assess the overall impact, and one similar to the CMAI to assess the frequency of the most problematic behaviors.

When considering any potential intervention, I first consider the risk and burden. I ask myself, "Is this likely to hurt my patient?" Then I consider the potential benefits, asking myself, "Could this meaningfully help my patient?" Then we engage in a risk-benefit conversation that is dyad specific, and it uses a patient-centered and shared decision-making framework that discusses realistic expectations and the uncertainties regarding risks, benefits, side effects, alternatives and trade-offs, and how we would measure and monitor or adjust the interventions as time goes on.

So how would I envision the potential impact of brexpiprazole in my patients? Well, I link the brexpiprazole results for efficacy similar to a 20-point within-patient reduction in the mean CMAI achieved for some patients in the study -- so the meaningful improvements in the CGI have about

2 points -- and I think about the potential impact that could have on preventing some of my dyads from going into a downward spiral and a clinical and psychosocial tipping point.

For the two patients that I just described, reducing the frequency, severity, duration, or diffusability of the most troubling and volatile symptoms, evaluated as a global impression of change, and improving this by even one CGI point could have meant the difference between their caregivers being able to cope/manage them safely, or as it turned out, not.

It would have made a critical difference if for the first patient I described, the glaring and grabbing episodes could have been reduced from, let's say, weekly or bi-weekly to keep him at home, or if the episodes would have been shorter lived, less intense, or easier to diffuse, or for the group home, they would have just remained at about the same weekly frequency.

For my second patient, if the resistiveness, combativeness, hitting, scratching, screaming when

approached for hygiene, and later which escalates to include medications, food, and water when she was more confused; if these agitated behaviors didn't occur multiple times a day and almost every time when she was approached, but allowed for just even once or twice daily when she could be properly cleaned and changed, hydrated, fed.

For both of these patients and many like them, if we can achieve the calming without oversedation, the Parkinsonism and cognitive suppression, allowing for more positive interactions, better care, and treatment of co-morbid conditions, and avoidance of the dehydration and malnutrition, and can reduce, even modestly, the frequency and the impact of the most problematic behaviors, I think we would over weeks and months be able to achieve cumulative and very meaningful benefits for some dyads, to decrease their burden, and their distress, and their burnouts, and to keep everyone farther away from a devastating tipping point.

In summary, brexpiprazole is a treatment option we need to improve care for patients and

families impacted by AAD. I believe the totality of evidence demonstrates consistent efficacy across multiple measures of agitated behaviors, and I believe it supports a better tolerability profile than current options.

I overall would regard the study efficacy results as moderate as reflected by the between group's Cohen's d standardized effect size point estimates that range between 0.25 and 0.35. I also view these data and differences to be clinically meaningful and beneficial, especially on an individual level when I consider the potential for the substantial benefits that were observed within patient changes, as reflected by a 50 percent greater likelihood that any given patient may benefit from a large 2-point CGI improvement.

I believe the tolerability and safety profile of brexpiprazole would allow patients to remain on the treatment sufficiently long enough to have the opportunity to receive benefits. It has a low incidence of severe and serious AEs and a low risk for sedation, conscious suppression, Parkinsonism,

and falls. I think, importantly, many treating clinicians may have experienced or can rely on a well-known tolerability and safety profile for brexpiprazole. The tolerability and safety profile, along with a favorable risk-benefit profile, I think would give me confidence to be able to recommend brexpiprazole to my patient and caregiver dyads as a treatment option in appropriately selected patients.

We desperately need to stop solely relying on off-label treatment options. Our field very much needs FDA-approved products that are favorable and well-defined efficacy and safety profiles and that have clear dosing directions and define populations for appropriate use. I don't consider brexpiprazole as a cure or a magic bullet for AAD, and I would not provide this expectation to my patients and families, but I do believe it offers a much needed viable and safe option where there remains a significant unmet need, helping many patients and dyads to cool down to below their boiling point and before reaching a tipping point.

On a personal level, I lived through

agitation aggression in AD dementia with my father and with its impact and consequences. It was one of the hardest, if not the hardest, thing I've had to go through. And even as a dementia subspecialist, I found myself in a quandary and a no-win situation without good options, and I felt despondent and powerless against it.

So overall, I would greatly welcome the opportunity to add brexpiprazole to my treatment armamentarium for agitation related to AD, and I believe that many of my colleagues, patients, and families would also feel similarly, and would very much want to have a choice in this option. Thank you very much for your attention. Let me return the lectern back to Dr. Hobart.

Applicant Presentation - Mary Hobart

DR. HOBART: Thank you, Dr. Atri.

Let me close with a summary of brexpiprazole's favorable benefit-risk profile. Across the clinical program, brexpiprazole showed substantial evidence of efficacy in multiple measures of agitation where non-pharmacological measures had

failed. Efficacy was demonstrated across the three main factors on the CMAI scale, and importantly, these results were clinically meaningful.

The safety profile of brexpiprazole in AAD is consistent with the known safety profile of the product in other indications, and as shown in our extension study, prolonged use of brexpiprazole was well tolerated with no new safety events identified. The mortality rate was low despite the higher number of deaths on brexpiprazole compared to placebo, and importantly, there were no apparent relationships between exposure to brexpiprazole and increased mortality.

Brexpiprazole addresses a high unmet medical need, and could be the first FDA-approved treatment for agitation in Alzheimer dementia. This would be the first time clinicians would have data to make informed choices in a high-risk patient population with limited options. We look forward to working with the FDA to provide labeling that will guide prescribers on the appropriate use of brexpiprazole in elderly patients with dementia.

Thank you for your time, and we would now be happy to address your questions.

Clarifying Questions to Applicant

DR. NARENDRAN: We will now take clarifying questions for Otsuka Pharmaceutical Company. 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 again 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 you wish and the slide number, if possible.

Finally, it would be helpful to acknowledge at the end of your question a thank you and end of your follow-up questions as well, so we can move on to the next panel member.

Our first question is from Dr. Apostolova.

DR. APOSTOLOVA: Hi. Liana Apostolova, Indiana University. This question is probably for Dr. McQuade.

Besides measuring agitation severity frequency, did you have any quality of life and caregiver burden measures in the trials?

DR. HOBART: Thank you.

Dr. McQuade?

DR. McQUADE: Thank you. In the first two studies, we did have some caregiver evaluations. The data were not particularly compelling. In the third study, we decided to remove those in an attempt to reduce placebo responding. Independent of the studies, our quality group, our health economics and outcomes research group, did do a separate survey study, and I'll ask my colleague to present the results to you to further address your question.

DR. APOSTOLOVA: Thank you.

MS. AGGARWAL: Good morning. Jyoti Aggarwal, director of Global Value Real-World Evidence at Otsuka. What we conducted was a real-world study that was intended to look at the relationship between the CMAI total score and caregiver outcomes. Specifically, we looked at the relationship between CMAI total score and the burden interview, as well as

the PHQ-4, to evaluate the relationship between CMAI total score and both the likelihood of depression and generalized anxiety disorder.

So based on the analysis from 250 caregivers, we found that the CMAI total score was associated with a -- or 1 5-point change in the CMAI total score was associated with 19 percent reduction in the likelihood of having high level of caregiver burden, as well as an 11 percent reduction in the likelihood of having a caregiver depression, and a 7 percent reduction in the likelihood of having caregiver anxiety or generalized anxiety disorder.

DR. APOSTOLOVA: Thank you. I don't have more questions.

MS. AGGARWAL: Perfect.

DR. HOBART: I believe we were attempting to display a slide. I'm not sure if you were able to see that. If you could confirm on your end whether you could see the slide.

There it comes, and that is just characterizing the data that was presented, but we wanted to allow you the opportunity to see it as

well.

Did that answer your question?

(No audible response.)

DR. HOBART: Thank you.

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

DR. WEISMAN: Hi. Thank you so much for the presentation. My question, I have a couple of them.

Were pharmacogenetics done, any polymorphisms of CYP genes, with relation to safety outcomes? And I guess that's for Dr. Kraus.

DR. HOBART: Dr. Kraus?

DR. KRAUS: Thank you for your question. We have not done pharmacogenetic evaluations within the context of this study population compared to safety outcomes in this study.

DR. WEISMAN: Then my second question as a long shot, did any deaths go to pathology? I'm particularly interested if any of the people had evidence of dementia with Lewy bodies with increased sensitivity to these drugs.

DR. KRAUS: I can't provide now whether any

of these patients went to autopsy. Most of the causes prior to death were fairly well established, but can ascertain after the break if any autopsy was done.

DR. WEISMAN: My final question is, have there been other studies in elderly subjects with schizophrenia and depression? Do we see increase deaths in those populations or is it really siloed within Alzheimer's?

DR. KRAUS: Across the brexpiprazole program, including Alzheimer's disease with agitation, rates of deaths are low. I'll put up a slide here for your reference.

As you know, we are approved for schizophrenia and adjunctive treatment with major depression, and the current program is referencing AAD. The overall incidence of deaths across these programs are, as you can see, 0.9 percent, 0.3 percent, 0.1 percent, respectively, with no common etiology around the causes of death. And for us, it's not necessarily surprising that the rates would be a bit higher in AAD given the patient

population.

DR. WEISMAN: Thank you very much.

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

DR. CUDKOWICZ: Thank you. Mert Cudkowicz, Harvard Medical School. I had just two questions.

One is, I was wondering if you might pull up the slide comparing the mortality with other antipsychotic drugs because it just went by real fast. I was trying to understand the reason for deaths, in general, with antipsychotics, and then the duration. Do you usually see it acutely or longer term?: And if it's more longer term in those other studies, do you have longer term follow-up from 283 and 284? Maybe someone can explain that a little bit more.

DR. HOBART: Dr Kraus?

DR. KRAUS: Thank you for your question. In terms of the comparative slide with the other antipsychotics that you referenced -- I'll pull that up right here for the committee's reference again -- a couple of points taken into consideration.

Typically, these were also studies of a similar duration, 12 weeks approximately, in terms of a population that was Alzheimer's or with dementia, primarily psychotic symptoms, but a subset, depending on the assessment, was agitation as well. It's also important to note that this is a historical comparison, so these studies having been done many years ago compared to our studies with brexpiprazole.

I do also want to say that in our program, as I mentioned earlier, we did have an extension to Study 213. When looking at the first phase where the deaths occurred, as I stated earlier, there was no pattern seen in terms of time of onset of deaths among these patients, and when we extended treatment out for a further 12 weeks, we saw no new deaths, including patients switching from placebo to brexpiprazole or continuing on brexpiprazole.

So at least with brexpiprazole, for that 24-week period, the data that we've presented today are probably most informative.

DR. CUDKOWICZ: Thank you very much.

I have other questions, but I might let the

other panelists ask, and I can circle back. Thank you.

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

DR. PAGANONI: Hello. Thank you very much. Thank you for the presentation. I also have several questions, and I'll start with one. I have a question about safety, so I think this is for Dr. Kraus.

You mentioned that, overall, adverse events were similar between the active and placebo groups; however, it seems to me that, at least numerically, there were a few more adverse events leading to discontinuation in the active group, so I wanted to ask if you could comment on that.

The other question I had is about drug-drug interactions. I noticed that a few medications were prohibited in the trial, but obviously some of them at least are widely used, and obviously polypharmacy is a concern, especially in the elderly population. So I was wondering, if this drug was approved, are you concerned that there may be interactions once the

drug is used in clinical practice, and how do you plan on monitoring safety?

DR. HOBART: I'll start with this a response, and then invite Dr. Kraus to comment further.

Brexpiprazole is primarily metabolized through the CYP2D6 and 3A4 inhibitor pathways, and we will have language in the label that will speak to recommended dose adjustments, which will be consistent with current labeling information. Specifically, the recommendation would be when using strong CYPD6 or 3A4 inhibitors to administer half the usual dose.

In regards to the question regarding further information on AEs that led to discontinuation, I'd like to invite Dr. Kraus to provide further details.

DR. KRAUS: Thank you, Dr. Hobart.

The majority of discontinuations due to AEs in these patients -- let me pull this up -- by system organ class were primarily in the lower dose group, psychiatric disorders, but also nervous system disorders, infections, and investigations or laboratory evaluations. We do see, when we look

across all brexpiprazole doses relative to placebo, that although drug is numerically higher, the rates are relatively low.

In terms of the preferred terms or having a little more detail beyond the system organ class in these three studies with all brexpiprazole versus placebo, to your point, overall, the discontinuation rate is higher based on AEs compared to placebo, 6 versus 3, but there really was not a kind of pattern of specific AEs that were identified in that group, as you can see on this table.

Does that answer your question.

DR. PAGANONI: Yes. Thank you.

DR. KRAUS: Thank you.

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

DR. THOMAS: Hello. Patrick Thomas from Baylor College of Medicine. Thanks for the presentation; one question about adverse events, and I believe this will be directed towards Dr. Kraus.

In the slide that you actually just showed, it looked like QTc prolongation was relatively low,

but in this population, in terms of the extent of prolongation, was it notable or not? Can you comment to that?

DR. HOBART: Dr. Kraus?

DR. KRAUS: Thank you for your question. In particular, related to QT prolongation, it was 0.3 percent versus zero, which represents, really, approximately 2 patients in the overall program. So it was 1.2 percent in the brex group versus 0.5 percent in the placebo group. If we look at overall QT prolongation, beyond being defined as an AE, there was no trend in the incidences that were observed in the dosing, and actually I can put up some data for you to take a look at.

No brexpiprazole-treated patient had a QTc value of greater than 500 milliseconds by any correction method; 4 placebo-treated patients had a QTcB value greater than 500 in all these short-term AAD trials. So we conclude from these data that there was not a signal related to administration of brexpiprazole in regards to QTc prolongation.

Does that answer your question, sir?

DR. THOMAS: Yes. Thank you.

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

MS. WITCZAK: Hi. Thanks for your presentation. I have a question. Obviously, antipsychotics have a terrible impact on a patient's ability to function, think, and care about others. I understand that it's very troubling for the caregiver. I'm curious. When you did all your analysis, was there one on the quality of life for the patients? I see the caregiver, but was there anything about the the actual patient's caregiver? That's question number one.

Question number two is, when you look at all of the Factor 1/Factor 2 and all the various questions, did you look at which questions had the greatest sense of improvements? Were they aggressive or non-aggressive? Were they dangerous or not dangerous? Obviously, they got grouped in, but I'm wondering if there's one or two of them that actually lead to the majority of the improvement.

So those are the two questions, and I'm not

sure who it goes to. Thank you.

DR. HOBART: Thank you, and I will start the response and pull in my other colleagues as needed.

As was shown on the previous slide, there were some patient outcomes that were collected as far as hospital admissions, emergency room visits, or falls in the real-world study that was previously shared, so both the patient and the caregiver outcomes.

Does this address the question?

MS. WITCZAK: Actually, it was more like quality of life, because we know what atypicals can do for somebody where sedated. Do we get into more of the quality of life? Obviously, when I look at emergency rooms, of course those are outcomes, but quality of life specifically, and did those kinds of questions get asked in the analysis?

DR. HOBART: So I'd like to invite Dr. McQuade to provide further information on quality of life.

DR. McQUADE: Thank you. As I mentioned previously, in the third study, we did not collect

quality-of-life data in an attempt to reduce placebo responding. As I mentioned, in the first two studies, we did collect some data. The responses were relatively modest, and at the end of the day did not provide any clear evidence of an effect.

MS. WITCZAK: Thank you.

DR. HOBART: Then in regards to your second question regarding the individual behaviors, can I have the slide? Thank you.

Looking across the three studies, we did look at behaviors by the three factors of the CMAI: the aggressive behaviors; the physically non-aggressive behaviors; and the verbally aggressive behaviors. There was a consistent performance that favored brexpiprazole over the individual behaviors.

As a reminder, the CMAI does look at a number of different behaviors, 29 different behaviors. Not every behavior is present in every subject. There's a large amount of difference on an individual patient level regarding the behaviors that are displayed, but irregardless of the individual behaviors, we do see broad improvement across the various individual

behaviors, and I'm pulling up that slide now.

This slide shows the 29 individual behaviors of the CMAI. The top of the arrow is the frequency of that behavior at baseline. The bottom of the arrow is the frequency at endpoint, the dark blue is the data from the 2-and-3 milligrams from 213, and the light blue is the 2-milligram data from 283. And as you can see, there are improvements in all types of individual behaviors. Some do occur more frequently and some are near the floor of the scale or occurring less frequently in the trial.

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

DR. PAGANONI: Thank you. Thank you for the opportunity to ask another question. My other question is about clinical meaningfulness. I must admit, I'm struggling a little bit to fully understand the impact of the effect of this drug on patients and their families, and perhaps I have a clarifying question.

I think it's about your primary endpoint. I believe it's your slide 22. I don't use this

particular scale in clinical practice, so perhaps that's why I'm not fully understanding it. But I understand that the between-group difference, which was definitely reproducible across your different randomized trials, is really a delta of 3-to-5 points on the total score.

Now I understand that the total score ranges from 29 to 203, so it's kind of a wide range, and if I understand it correctly, the delta again is 3-to-5 points. But the total score comes from the summation of 29 items, with each item being rated 1 to 7, so I guess this change is really distributed across several items, 29 in fact.

So can you help me understand? I understand that the last presentation pointed to a significant change. For example, if you go from 6 to 4, basically, the frequency of that particular symptom decreases dramatically, which can be clinically meaningful but, again, the total delta is distributed across 29 points. Perhaps, I'm not fully understanding this scale, so I would appreciate your insights.

DR. HOBART: Dr. McQuade?

DR. McQUADE: Thank you. I think there are several questions in there that I'll try to get to. Let me start with your first question about clinical meaningfulness.

Again, these are the primary results from the two studies. In Study 213, in specific, when we used an enriched population, you can see that the p-value is less than 0.01, or less than 1 percent, indicating that these results are probably not due to chance or randomness. But I think more importantly than just looking at these graphs, it's important to look at response analysis. If you'll bear with me, I'll put up a couple of slides to support that.

Again, as you were mentioning, the change from baseline represents a population effect. I think at the end of the day, the more meaningful effect is what happens when you look at individual patients. When we look at individual patients and look at reduction in CMAI score from baseline, you can see that regardless of whether you look at a 20 percent reduction from baseline, a 30 percent

reduction, or a 40 percent reduction, more patients responded to brexpiprazole than to placebo, and the rates are between 40 percent more on the left and 60 percent more on the right.

We then went on to do another analysis by trying to correlate a meaningful within-patient threshold that's correlated to CGIS improvement of 2 points, and when we did that, you again see that 56 percent of patients responded to brexpiprazole compared to 37 percent of patients on placebo; again, about a 50 percent higher value. So using response criteria, we're able to state that 50 percent more of patients respond to brexpiprazole than placebo, and at the end of the day, I think that helps put some of the context into the population score of the CMAI total score.

Let me go on briefly. Many of these inventory scales in psychiatry that we use -- things like PANSS in schizophrenia, or MADRS in depression, or in this case, CMAI in agitation -- firstly, they don't get very much to near the top of the scale. As we showed here, the baseline score in the study was

about 80, whereas the maximal score is 203, and it would obviously be almost impossible for patients to get to 203, which would be several times an hour for every individual item.

So it's not unusual that we see this kind of phenomenon. Also, we did one other analysis that I'd like to share with you, and that is we looked at individual items and we grouped them by their baseline score. So on the left you have the individual items that occurred several times an hour for a score of 7, and as it goes across, you can see it reduces, obviously. The greatest effect we see are in the patients who have the most frequent behaviors, so again, a clinically meaningful improvement in this case from several times an hour to several times a week for those items that were rated as a 7 at baseline.

Did I miss anything in your question?

DR. PAGANONI: No, this helps. I must admit, I was surprised by the number of responders in the placebo group. So it seems like, overall, the natural history of this scale tends to improve over

the course of the 12 weeks of observation, if I understand the graphs correctly, although I am convinced that obviously you reproduced the treatment effect across different programs -- that I understand -- and the p-value supports that.

Again, I'm struggling a little bit in terms of the actual magnitude of change for the treated participants. The difference between the responders when you compare treated versus placebo, even some placebo participants improved.

DR. McQUADE: This is clearly a problem we have across psychiatry. We've seen a number of cases where placebo responding is extensive, and in fact -- we don't need to call up the data -- there's even a study showing that in schizophrenia, placebo responding went from going 2 points worse from baseline to 15 or 16 points better than baseline over the course of a 20-year period. So placebo responding is clearly a problem in our psychiatric studies.

Actually, my colleagues were able to pull it up. I'll just put it up briefly for you to see.

Again, this is just placebo responding, and you see that it increases in a linear fashion over time; so a problem we have to face. At the end of the day, I think the reproduction and the response rate is what's important.

One other comment, however, is that as we conduct these studies, this is not very consistent with real-world practice for these patients. Patients have 2-and-3 hour sessions with clinicians. They get a lot of attention and a lot of care, and a lot of that helps drive placebo responding in the clinical trial setting, whereas it's something that is somewhat less pronounced in the real-world setting.

DR. PAGANONI: Thank you.

DR. HOBART: I'd like to invite Dr. Atri to also share his clinical perspective on your question.

Dr. Atri?

DR. ATRI: Thank you for your question. I think it's a really important one. We can bring this slide up that I put up. Thank you.

So there are obviously many different ways of

thinking about meaningful benefits, and one of the main things that I was thinking about is that, to me, the results were consistent and believable for the population, but I went back to the Cohen's d effect sizes because most people wouldn't appreciate -- many of us don't use these these scales, so putting it on the same metric, a Cohen's d of 0.25 to 0.35 tells me there's a moderate effect there for the population.

But then digging deeper, I really think about this responder of am I going to give some of my patients potentially a greater chance at something very meaningful for that? And that's where that 50 percent more likelihood for any given patient comes in, and that's for a 2-point change. So a 20-point change in the CMAI, kind of correlating with a 2-point change in the CGIS, takes somebody from markedly ill to mildly ill related to their agitation. That's a lot you easier to cope with over time. Even if it's more modest than that, taking them from markedly to moderately, some of these patients are really at stages where they're just are. They're kind of like stewing a little bit. We just

don't want them to boil over. And for that reason, even that 1-point change could actually be quite meaningful.

It's only going to help some of the patients. Is it going to give 1 out of 5 of my patients a possibility for this, or 1 out of 3? I think the data supports that, and that's one of the ways that I look at meaningfulness here.

DR. HOBART: Thank you.

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

DR. CUDKOWICZ: Thank you. It's kind of an extension of what we're talking about. You show clearly, I think, that there's a large majority of the participants who responded. I wanted to ask a little bit if you have some insight on why people might not respond versus who responds better. You might have alluded to it related to the severity of the scale, but anything that would help clinicians decide if there might be a group of people, for example, that they wouldn't try this for, or the opposite, that there is a group of people they would

really want to try this for.

Maybe related to that, I'd like to hear from Dr. Atri. How will you actually prescribe this? Would this be something that you'd continue until the person has very little agitation or would you withdraw it? And if you withdraw it, are there any worries about that?

DR. HOBART: Dr. Atri?

DR. ATRI: Thank you, Dr. Cudkowicz. I would say this is not for every patient; it's for appropriately selected patients. Depending on, again, that initial shared decision making that we have, we're going to monitor it over time, and depending on the particular clinical, psychosocial, environmental, and cultural considerations, we're going to adjust that plan.

The idea is to continue that iterative process and always give the minimal dose that's going to be effective, and then look at potentially withdrawing and titrating down. But it's going to really depend on that particular situation with a patient and caregiver dyad I think.

DR. CUDKOWICZ: And the other part of the question is about, do you have any data on who are the better or worst responders? That would be helpful for a clinician.

DR. HOBART: Dr. McQuade?

DR. McQUADE: Yes. I'd like to call back up a slide that I presented previously about the baseline severity. Thank you.

Again, as I think these data show pretty clearly, there's a bigger effect of drug on those symptoms that are more frequent. When we looked at subanalyses that also looked at baseline agitation levels, again, the same pattern emerged. There was a bigger drug effect and a bigger separation from placebo in patients with more moderate-to-severe agitation at baseline than at mild, also recognizing the floor effect of this particular scale, which makes some of the low-scoring patients at baseline very difficult to interpret.

DR. CUDKOWICZ: Thank you.

DR. HOBART: Dr. Ismail?

DR. ISMAIL: Thank you. I just wanted to

supplement Dr. Atri's response to the first question regarding duration of treatment.

The times when we treat someone with an antipsychotic, and then they're on it for good, are hopefully gone. And the standard of care is such that at 3 months, the very latest, we would reassess the efficacy and try to titrate down off of these medicines. They're not intended to be forever. The data from other studies show us that for some people, titration down is successful, at least to a lower dose, and for some, there is a clear return of symptoms, which then necessitates revisiting the situation, determining if the dose needs to go back up or the med needs to be restarted; but the practice and the standard of care are such that we have to revisit this very regularly. Thank you.

DR. HOBART: Thank you. That's helpful.

DR. NARENDRAN: I see a few more questions. We're almost getting closer to a break, so if you could make it short and short answers.

Dr. Apostolova, your question?

DR. APOSTOLOVA: Yes. It's great that I'm

following Dr. Cudkowicz because my question is, in a way, similar to hers. I wanted to know if there is any difference in how patients respond therapeutically based on the factors. As grouped in the CMAI, are any of the factors aggressive, verbally agitated, more or less responsive? Would that in any way guide our treatment with brexpiprazole in the future? Also, I wanted to ask, across those factors, were the groups balanced in terms of severity, placebo versus drug?

DR. HOBART: Dr. McQuade?

DR. McQUADE: Thank you, And can I ask my colleagues to also pull up the data from 213?

This is the pooled data across studies, looking at the three key factors of the CMAI. On the left is aggressive, in the middle is physically non-aggressive, and on the right is verbally agitated. You can see that in all three cases, there's nominal improvement with p-values less than 0.05, so we do see improvement in all the symptoms. And I think it's very important, because you wouldn't want to trade improvement in one type of symptom for

worsening of another.

I ask my colleagues to also bring up Study 13 because, again, as you recall, we enriched this population for patients with aggressive agitation at baseline. Even so, even so enriched, you still see the same pattern of improvement across all three of the subfactors. So it's a consistent finding in all of our studies that we see improvement across the board in all agitated behaviors, regardless of whether you look at all patients or those who are in the enriched population.

DR. APOSTOLOVA: So in follow-up to that, was there balance of matching severity between placebo and brexpiprazole based on a factor? For instance, were more severely aggressive patients on placebo as opposed to more verbally agitated patients on brexpiprazole, in terms of percentage of distribution of severity, if that makes sense?

DR. McQUADE: No, it makes perfect sense. There was complete balance between the placebo group and brexpiprazole. The randomization did its job. I will comment that the baseline scores for the

aggressive generally were a little higher, but that's based on the fact that there are more items in the aggressive factor than there are in the physically non-aggressive and verbally. It's sort of just that number of items that helps drive some of the baseline differences.

DR. APOSTOLOVA: Thank you.

DR. NARENDRAN: It seems like our time is up, so I'm just going to stop there. We could cycle back maybe if we have time for the last other questions that may be. So we'll take a quick 10-minute break. Panel members, please remember that there should be no chatting or discussion of the meeting topics with other panel members during the break. We will resume at 11:05 for the FDA presentations.

(Whereupon, at 10:56 a.m., a recess was taken, and the meeting resumed at 11:05 a.m.)

DR. NARENDRAN: Welcome back.

We will now proceed with the FDA presentations, starting with Dr. Shamir Kalaria.

FDA Presentation - Shamir Kalaria

DR. KALARIA: Thank you, Dr. Narendran.

Good morning, everyone. My name is Shamir Kalaria, and I'm the primary clinical reviewer from the Division of Psychiatry. I'll be providing FDA's assessment on the applicant's supplementary new drug application for brexpiprazole, for the treatment of agitation associated with Alzheimer's dementia, also referred throughout this presentation as AAD.

I'll begin this presentation by providing a brief overview of the application, followed by a walkthrough summary of the available evidence contributing to FDA's evaluation of efficacy and safety. I'll then provide our assessment of the application and several concluding remarks regarding our current understanding of brexpiprazole's benefit-risk profile to assist with our discussion today.

Brexpiprazole is an atypical antipsychotic drug that was initially FDA approved in 2015 for the adjunctive treatment of major depressive disorder and for the treatment of schizophrenia in adults. Although brexpiprazole's exact mechanism of action for the treatment of ADD and other psychiatric

conditions is unknown, its pharmacologic effect is thought to be exerted by a combination of partial agonist activity at serotonin subtype 1A and dopamine 2 receptors, and as an antagonist at the serotonin subtype 2A receptor.

The applicant's proposed indication for the supplementary new drug application is for the treatment of agitation associated with Alzheimer's dementia, with a recommended dose range between 2-to-3 milligrams per day. The brexpiprazole AAD clinical development program consisted of three double-blind, placebo-controlled, 12-week studies. Throughout this presentation, I'll be referring to them to as Studies 283, 284, and 213.

Although all three phase 3 studies share the basic trial design element, differences in the study population, including the diagnostic criteria for probable AD and agitation, can be attributed to the agency's evolving advice over time. Of note, the applicant initiated Studies 283 and 284 back in 2013 and study 213 in 2018.

The applicant also conducted Study 211, an

observational post-treatment in subjects who completed Studies 283 and 284, and one active extension treatment study, also referred to as Study 182, that evaluated brexpiprazole for an additional 12 weeks in subjects who completed Study 213.

In November of 2012, the agency met with the applicant during a pre-IND meeting to discuss the development plan and the feasibility of pursuing an indication for the treatment of AAD. Even though the applicant was still undecided whether they were planning to target a broad population of patients with Alzheimer's dementia and agitation or a more specific indication for the treatment of aggressive agitation in patients with Alzheimer's dementia, the agency agreed that agitation in itself is clinically recognized as an important aspect of AAD and a potential target for treatment.

At this time, the applicant proposed a clinical development program consisting of two phase 3 studies evaluating institutionalized and community-dwelling subjects diagnosed with probable

AD. For both studies, the applicant proposed to use the Cohen-Mansfield Agitation Inventory, also known as the CMAI, as the primary efficacy endpoint. Because the applicant did not settle on a specific target population, the agency did not provide more specific advice and indicated that the general study designs appeared reasonable. The agency encouraged the applicant to also provide details on the use of the CMAI instrument throughout their program.

In early 2013, the applicant submitted their initial protocols for Studies 283 and 284 for review. After reaching agreement with the agency, the applicant initiated both studies later in that year. Both Studies 283 and 284 were designed as randomized, double-blind, placebo-controlled, multicenter studies of 12 weeks in length, intended to evaluate the efficacy, safety, and tolerability of brexpiprazole in AAD.

Study 283 was a fixed-dose study design, evaluating brexpiprazole dosing regimens of 1 milligram and 2 milligrams per day relative to placebo. The applicant originally included the

0.5-milligram per day arm, but later dropped the arm from the efficacy analysis based on data collected from prior studies that suggested that the dose might be ineffective.

Study 284 was a flexible-dose study design, evaluating brexpiprazole dose ranges between 0.5-to-2 milligrams per day. Each study consisted of a screening period for up to 42 days to assess eligibility criteria and to wash out prohibited medications prior to randomization. Each study also included a 12-week, double-blind treatment period and a 30-day safety follow-up evaluation for each subject after receiving their final dose of their medication. For all subjects who terminated early from the study, the subject's caregiver was contacted at week 12 to collect mortality status information.

Both trials included identical eligibility criteria. The applicant enrolled subjects 55-to-90 years of age living in either an institutionalized or non-institutionalized care setting. To establish a probable diagnosis of AD, the applicant utilized the NINCDS-ADRDA criteria.

Subjects also had to exhibit mild-to-severe cognitive impairment, defined as a Mini-Mental State Exam, of between 5 to 22 points.

For both studies, the applicant also included subjects with significant agitation, defined as an NPI agitation and aggression subscore of at least 4, with symptom onset at least 2 weeks prior to screening. Subjects required a previous trial of non-pharmacologic interventions to treat symptoms of agitation. Subjects that reported an insufficient response to at least two previous antipsychotics were not included in these studies.

Prior to 2015, there was no commonly accepted definition for agitation. Studies often utilized lay definitions that were nonspecific and included states of excitement, disturbance, or worry. In 2015, the International Psychogeriatric Association, also known as the IPA, formed the Agitation Definition Working Group to establish a consensus definition of agitation that would facilitate a wide spectrum of research and provide a common framework for diagnostic nomenclature. Recently, the working group

finalized the IPA provisional definition for agitation with minimal modifications.

Study 283 and 284 were initiated in 2013, a few years before the creation of the IPA provisional definition. Although there was no clinically accepted definition at the time, the inclusion criteria of the subjects with agitation non-attributed to another illness, and for at least 2 weeks, and the use of the NPI scale to identify subjects with significant symptoms of agitation, closely resembled the criteria outlined in the IPA definition. Therefore, the results of these studies may be generalizable to a population that meets the current IPA consensus definition. Similarly, the applicant included subjects with probable AD mild-to-severe cognitive impairment. At the time, probable AD was based on the NINCDS definition and was thought to be reasonable due to a current lack of biomarker-based diagnostic criteria.

Since this program was initiated, the science in our field has evolved and our current regulatory understanding has changed. Currently, the agency

recommends sponsors to follow the 2018 Draft Guidance for Industry and the 2018 National Institute of Aging criteria to identify subjects with AD. Our current regulatory advice for these programs also include enrollment of subjects that are generalizable to the real-world population. Therefore, the inclusion of subjects with mild-to-severe cognitive impairment reflects a range that's likely for patients that have AAD.

This table provides the randomization ratios for each of the studies and the titration schemes employed. For Study 283, the titration scheme followed a force titration to target dose approach, while Study 284 utilized the flexible-dose titration criteria, where subjects were titrated up from 1 milligram per day to 2 milligrams per day after week 4, based on response and tolerability. To emphasize, each of these studies evaluated chronic once-daily dosing of brexpiprazole over 12 weeks.

During the initial pre-IND meeting, the applicant proposed to use the Cohen-Mansfield Agitation Inventory, also known as the CMAI, as the

primary efficacy measure for both phase 3 studies. The CMAI is a caregiver-reported instrument that consists of 29 items that rate symptom frequency on a scale between 1 to 7, with 1 being the best rating of no occurrence and 7 being the worst rating of multiple occurrences a day.

The CMAI total score is the sum of ratings from all 29 items and could range from a possible of 29 to 203 points, and a large scale factor analysis of the CMAI conducted in nursing home patients revealed four major CMAI subscales, including aggression, physically non-aggression, verbal agitation, and hiding and hoarding.

This table provides the individual items that loaded onto each of the subscales with their respective possible score range. Five other items, including making strange noises; intentionally falling; eating or drinking inappropriate substances; and verbal or physical sexual advances did not load into a specific domain and are characterized as unloaded items.

From a clinical perspective, agitation

represents a continuum of behaviors, with one end of the spectrum representing milder, non-threatening behaviors such as verbal agitation, and the other consisting of aggressive behaviors that may cause harm to self or others. In addition to symptom severity, frequency with which these behaviors are exhibited play an important role in deciding which treatments are needed. For agitated behaviors that are milder and non-threatening, there may be a higher frequency threshold before treatment interventions are considered, as compared to those with more threatening behaviors, which may require a lower frequency threshold. Therefore, from a regulatory perspective, not only were we interested in understanding the treatment effect on the total score, but we are also interested in evaluating movement on these subscales.

For both trials, the primary efficacy endpoint was changed from baseline in the CMAI total score at week 12, while the multiplicity adjusted secondary endpoint was changed from baseline in the Clinician Global Impression of Severity, also known

as the CGIS, score at week 12. The applicant also conducted several exploratory analyses on various psychiatric and quality-of-life measures. To further explicate the findings from the primary efficacy endpoint, this presentation will focus on the treatment effects for each of the three major CMA subscales that closely align with the diagnostic criteria for agitation.

Because the CMAI is a caregiver-reported outcome measure, the applicant included several caregiver requirements. The caregiver was identified as a person who had sufficient contact to observe and describe the subject's behaviors. The recommended minimum level of contact between the caregiver and the subject was at least 2 hours per day for 4 days a week. In the non-institutionalized care setting, the subject's caretaker was the person who lived with and cared for the subject on a regular basis, and may not necessarily be the same person who fills the role of the caregiver. In the institutionalized care setting, the caregiver could be a staff member or another individual, including a family member or a

hired professional.

For each study, the evaluation of the primary efficacy endpoint was based on the mixed model's repeated measures analysis. The MMR model adjusted for prespecified covariates, including treatment, trial center, visit week, and also included interactions for the treatment by visit and baseline CMAI total score by visit. The same methodology was also used to evaluate the secondary efficacy endpoint.

The applicant also used a hierarchical testing procedure to control for type 1 error rate. Specifically, for Study 283, the primary efficacy endpoint was tested first by comparing the brexpiprazole 2-milligram arm versus placebo, and then a comparison of the brexpiprazole 1-milligram arm versus placebo. If the primary efficacy analysis for the CMAI total score yielded statistically significant results for both comparisons, the applicant repeated the hierarchical testing procedure for the secondary endpoint.

Now moving on to the results for Study 283,

the applicant randomized 433 subjects into the double-blind treatment period to receive either placebo, brexpiprazole 0.5 milligram, 1 milligram, or 2 milligram per day. As mentioned before, the brexpiprazole 0.5-milligram treatment arm was dropped from the efficacy analysis due to previous findings that suggested that the dose might be ineffective. The most frequent reason for study discontinuation across all treatment groups was due to adverse events.

The efficacy population consisted of mostly white, non-Hispanic subjects with a mean age of 74 years. Most subjects resided in an institutionalized care setting and exhibited either moderate or severe cognitive impairment, and approximately 26 percent of patients also exhibited co-morbid psychotic symptoms. When evaluating the CMAI item at baseline, approximately 70 percent of subjects also exhibited significant symptoms across all three domains of agitation.

The results of the primary and secondary efficacy analysis are displayed on this table. I

want to highlight that a statistically significant treatment effect for only the brexpiprazole 2-milligram per day arm versus placebo was observed at week 12 for the primary efficacy measure; however, the treatment difference did not reach statistical significance for either of the brexpiprazole arms for the secondary efficacy endpoint on the CGIS score.

The figure on the left provides a visual representation of the time course of response for the change in the CMAI total score over 12 weeks. The longitudinal response profile suggested numerical separation between the brexpiprazole 2-milligram arm versus placebo, starting after 4 weeks of treatment that also appeared to be sustained throughout the treatment period.

Now let's take a step back to the initial pre-IND meeting in 2012. At the time, the agency agreed to use the CMAI total score as a primary efficacy measure and thought it was reasonable for both Studies 283 and 284. However, it's important to note that different agitated behaviors occur in different circumstances and in different people.

Because of this heterogeneity, the developers of the CMAI did not intend to use the total score of all 29 items. As a reminder, the agency and the applicant did discuss the need for consistent directional improvements in the three major subscales of agitation and were interested to see whether improvements in one of the subscales was compensated by worsening in another.

Because some skills of aggression, physical non-aggression, and verbal agitation closely align with the behaviors outlined in the IPA criteria, this presentation will focus on these three subscales of interest. This table displays one of the applicant's secondary analyses based on the three major factor domains on the CMAI measure. As you can see, the placebo subtracted difference at week 12 in the brexpiprazole 2-milligram arm suggested consistent numerical improvement across all three subscales, with the greatest group mean effect exerted on the verbally agitated behavior domain.

Moving on to Study 284, in Study 284, 270 subjects were randomized into the double-blind

treatment period. Similar to Study 283, the most frequent reason for discontinuation was due to adverse events. Because Study 283 and 284 specified identical eligibility criteria, the demographic and baseline characteristics also appeared similar. The efficacy population, again, consisted of mostly white, non-Hispanic subjects with a mean age of 74 years. Most subjects resided in an institutionalized care setting and exhibited either moderate or severe cognitive impairment, and only 22 percent of subjects presented with co-morbid psychotic symptoms. Based on reported symptoms at baseline, again, approximately 70 percent of subjects exhibited significant symptoms of agitation across all three domains of agitation.

As you can see from this table, the results of the primary efficacy endpoint on the CMAI total score for Study 284 was not statistically significant. Because of the lack of a statistical significant finding on the primary endpoint, the results of the secondary endpoint analysis on the CGIS score is considered solely descriptive.

Again, the figure on the left provides the time course of response for the change in the CMAI total score over 12 weeks. In comparison with Study 283 that suggested a separation between brexpiprazole 2 milligrams per day versus placebo starting at 4 weeks, the longitudinal response profile for Study 284 shows a separation between flexibly-dosed brexpiprazole and placebo, starting at 6 weeks, that remains throughout the study period.

When we take a closer look at the changes in the CMAI subscale, the placebo subtracted difference at week 12 in the brexpiprazole arm was numerically greater relative to placebo across all three major subdomains. However, unlike Study 283 that suggested greater effects on verbal agitation, the brexpiprazole group in Study 284 appeared to exert its greatest effect on the aggressive behavior domain.

Although Study 284 failed to meet its primary endpoint, the applicant conducted several post hoc exploratory analyses to further evaluate treatment response among subjects who received brexpiprazole

2 milligrams per day. At the week 4 visit, approximately half of the subjects in both treatment arms required an increase in dose from 1 milligram per day to 2 milligrams per day. For the primary efficacy endpoint, a numerical improvement was observed with the brexpiprazole group over placebo among the subgroup of patients whose dosage was increased to 2 milligrams per day.

When evaluating the subgroup of subjects who did not require a dosage increase at week 4, there was no numerical difference between treatment arms. These results were also similar when comparing treatment arms by modal dose, where subjects with a modal dose of at least 2 milligrams per day exhibited a numerical improvement with brexpiprazole over placebo. These post hoc exploratory analyses in combination with the results with Study 283 could further suggest that the minimum effect of brexpiprazole dose for AAD is likely 2 milligrams per day.

During a 2017 guidance meeting, the applicant shared these results from Study 283 and 284,

including post hoc analyses, that suggested a treatment effect among subjects with significant aggressive behaviors at baseline, and among subjects that received brexpiprazole 2 milligrams per day after week 4, suggested a robust treatment effect. On its own, the agency did not consider Study 283 to be statistically persuasive, and emphasized that post hoc analyses could not serve as a primary support for a potential indication.

The agency recommended the applicant conduct another 12-week, double-blind, placebo-controlled study to evaluate a higher dose than what was previously studied. The agency also advised that the subjects do not necessarily need to exhibit aggressive behaviors to be suitable for enrollment, and recommended that the applicant use the existing IPA consensus definition for agitation to ensure enrolled subjects exhibited significant agitation at baseline.

In February of 2018, the applicant met with the agency again to discuss key trial design elements for Study 213. Previously, the agency noted that the

use of the NPI agitation and aggression score of at least 4 likely led to the enrollment of some patients with limited or very mild agitation. The applicant hypothesized that, including subjects with significant aggressive behaviors listed in the CMAI Factor 1 could lead to a potential increased treatment effect. Although the applicant proposed enrichment strategy appeared to be justified based on their post hoc analyses, the agency was unclear at this time whether the study results would be generalizable to patients with non-aggressive symptoms and cautioned the applicant that narrowing the target population could narrow the product's final indication for use.

The applicant also stressed difficulties in subject recruitment and proposed to combine the brexpiprazole 2-milligram and 3-milligram per day arms for the primary analysis. Since this would be the only source of information for higher doses of brexpiprazole in elderly patients, the agency recommended that the applicant enroll at least 100 subjects to receive brexpiprazole 3 milligrams

per day. The agency also agreed that a long-term safety study would not be a pre-approval requirement, but could be a phase 4 commitment.

The applicant submitted their initial protocol for review in 2018, and the proposed study design was similar in study length and timing of assessments relative to Study 283 and 284. Study 213's population was also similar to Study 283 and 284 with a few caveats. The inclusion of criteria of enrolling subjects with a probable diagnosis of AD was still based on the NINCDS criteria, and subjects still needed to meet the requirements for mild-to-severe cognitive impairment.

In addition to these requirements for agitation onset and symptom severity based on the NPI agitation and aggression subscore, the applicant adhered to the agency's advice to require subjects to meet the 2015 IPA provisional consensus definition for agitation. The applicant also proceeded with their proposed enrichment criteria for including subjects with significant aggressive behaviors at baseline.

The statistical model to analyze the primary and secondary endpoints was also similar to Study 283 and 284; however, in this study, the applicant also incorporated an unblinded interim analysis to potentially terminate the trial early for efficacy after the first 255 subjects who were randomized either completed or terminated the study. After reviewing the results of the unblinded interim analysis, the primary efficacy endpoint was tested at a two-sided, 3.5 percent nominal significance level for the analysis to control for overall type 1 error rate.

Now moving on to study results for Study 213, in Study 213, 345 subjects were randomized into the double-blind treatment period, and similar to the two previously discussed studies, again, the most frequent reason for study discontinuation was due to adverse events. The efficacy population consisted of, again, mostly white and non-Hispanic subjects with a mean of 74 years. Compared to Study 283 that included 16 percent of Hispanic subjects, and Study 284 that included less than 6 percent of Hispanic

subjects, the Hispanic subject population almost accounted for a third of this total study population for Study 213.

This study also included more subjects in a non-institutionalized care setting than the two previous studies. Even though the study was enriched for subjects with significant aggressive behaviors at baseline, approximately 90 percent of subjects exhibited significant symptoms across all three domains of agitation. Based on the results of the study, the combined brexpiprazole 2-and-3 milligram group demonstrated a statistically significant improvement versus placebo on both the primary and secondary efficacy analyses.

The figure on the left provides the time course of response for the change in the CMAI total score over 12 weeks. The longitudinal response profile similarly suggests the separation of the treatment effect starting at 4 weeks of treatment. Additional analyses were conducted by the applicant to evaluate the individual treatment effects of the brexpiprazole 2-milligram and 3-milligram arms

separate. Reductions in the CMAI total score and the CGIS reached nominal statistical significance for both the brexpiprazole 2-milligram and 3-milligram arms when analyzed separately.

Further evaluation of the CMAI subscales also indicated a nominally significant improvement with brexpiprazole over placebo that was consistent across all three domains. Similar to Study 284, brexpiprazole exerted its greatest effect on the aggressive behavior domain.

Overall, the brexpiprazole clinical development program for AAD consisted of three adequate and well-controlled trials intended to provide substantial evidence for effectiveness. Based on the study results, the applicant demonstrated a statistically significant treatment effect with the brexpiprazole 2-milligram group in Study 283 and with the combined brexpiprazole 2- and 3-milligram groups in Study 213. Although Study 284 failed to meet its primary endpoint, the study did provide supportive evidence of efficacy by showing that the treatment effect among subjects titrated to

brexpiprazole 2 milligrams was nominally significant relative to placebo.

This observed treatment effect was also numerically similar to the results with the brexpiprazole 2-milligram group shown in Studies 283 and 213. Additional exploratory evaluation on the CMAI factor subscores also indicated nominally consistent trends in the improvement in physical, aggressive, non-aggressive, and verbally agitated behaviors. Although the applicant enriched Study 213 to include a study population that exhibited aggressive behaviors at baseline, subgroup analyses suggested that the treatment effect was also present among subjects who exhibited significant physically non-aggressive and verbally agitated behaviors.

In comparison with the current literature, trials evaluating other antipsychotics and alternative treatments for AAD suggest very limited evidence of efficacy with serious risks and tolerability concerns. Specifically related to this application, the benefit-risk analysis for brexpiprazole in AAD requires weighing the observed

benefits against the recognized risks of mortality in elderly patients with dementia-related psychosis. Therefore, to better contextualize the underlying mortality risk associated with brexpiprazole, a juxtaposition of findings from this program and FDA's previous meta-analysis of antipsychotics is needed.

The safety evaluation for this application is primarily based on the three previously mentioned studies. In addition, the applicant conducted two additional safety studies, a 2-month observational post-treatment rollover study and a 12-week active treatment extension study. Given the current boxed warning and to better understand brexpiprazole's risk for mortality, the review team primarily focused on deaths observed across all phase 3 studies. A review of safety also consisted of an evaluation of adverse events, laboratory assessments, and other safety findings to compare with the known safety profile observed in adults with schizophrenia and major depressive disorder.

In the early 2000s, the FDA received several reports of serious cerebrovascular adverse events and

issued warning statements for several antipsychotic product labels. Given the number of reports and the growing concerns, the agency conducted a meta-analysis to systematically assess the available data to determine the magnitude and consistency of the reported mortality risk.

The agency's 2005 meta-analysis included 17 randomized, short-term, placebo-controlled trials of five atypical and one typical antipsychotic in elderly patients with dementia. The database included approximately 5400 subjects, 3600 of which were randomized to active treatment and 1800 of which received placebo. The average age of subjects included in the database was approximately 81 years, and with regards to study duration, 7 out of the 17 studies evaluated treatment over 10 weeks, and four of the studies were 12 weeks in length.

The meta-analysis revealed a 70 percent increased risk of death in subjects treated with an antipsychotic versus placebo. Over the course of a 10-week trial, the rate of death was 4.5 percent among the drug-treated group versus 2.6 percent in

the placebo-treated group. Although the causes of death vary, most of the deaths appear to be either cardiovascular or infectious in nature. Because there are a limited number of well-defined cases, the specific mechanism by which these antipsychotics increase the risk of death still remains unclear.

Based on these data, the agency required a boxed warning for all second-generation antipsychotics in 2005, and later expanded the scope of the warning later in 2008 to all typical antipsychotics. Due to the higher incidence of stroke and transient ischemic attacks, the agency also included a class warning for cerebrovascular adverse events for all antipsychotics.

The graph on the left describes the cumulative hazard of death over time, based on subjects included in the 2005 database. As you can see, the hazard of death appears to be persistent over the course of 100 days and proportional between the two groups. When looking at the figure more closely, the lack of concentration of deaths closer at the time of drug initiation suggests that

antipsychotics may not be the direct cause of death, and instead, the steady rise in the cumulative events with a higher rate in the antipsychotic group versus placebo rather suggests an indirect effect on death due to exogenous causes.

By assessing the timing of death relative to adverse events and drug exposure, the previous data suggest that the drug was not usually the direct cause of death but may be associated with worsening outcomes. As commonly seen with antipsychotic trials in elderly patients, adverse events are a common reason for dropout. Non-fatal adverse reactions to drug could prevent subjects from further study participation and still increase the risk of death over time.

Even though there's little ambiguity in recognizing death, there's often difficulties in deciding which deaths are relevant and in gathering accurate mortality data in subjects that become lost to follow-up. Therefore, it is important when conducting mortality analyses in these contexts that an appropriate sampling time frame to count deaths is

specified in order to accurately estimate the risk of mortality.

This visual example provides further highlights to a potential bias associated with incorrectly specifying a sampling time frame when counting deaths. In this hypothetical example, we're using a similar trial design where subjects were randomized to drug or placebo and were evaluated over a course of a 12-week trial. Similar to the previously discussed trials, this example also includes a 30-day follow-up assessment after the last dose of study medication.

I'll walk you through two scenarios where the subject received placebo and active treatment, and in both scenarios, the subject is destined for death at day 84. Patient A in blue is randomized to receive antipsychotic, but experiences an adverse reaction that causes them to drop out at day 30. Because of the follow-up, investigators reassess the subject 30 days after the last dose of study medication, which in this case would be at day 60. If we were to use the sampling time frame of 30 days after the last

dose of medication to count deaths, this death would not be counted in the drug arm.

Alternatively, if the same Patient A was randomized to placebo, which is shown in gray, they would not have dropped out from the study due to drug-related adverse reaction, and would have received treatment for the entire duration of the study. When the subject dies at day 84, the death is then subsequently counted in the placebo arm. Therefore, the proposed sampling time frame for counting deaths up to 30 days after the last dose of study medication could artificially lower the background rate in the drug arm and underestimate the mortality risk. We aim to apply these principles to estimate the underlying mortality risks associated with brexpiprazole in this program.

Because each of the phase 3 studies consisted of a similar duration of treatment and follow-up observation period, the review team focused on deaths across all three 12-week phase 3 studies. Across the three studies, the applicant reported a total of 9 deaths; 8 subjects received brexpiprazole and

1 subject received placebo. The applicant also reported one death in a subject that was enrolled in Study 211 that previously received brexpiprazole in Study 284. There were no deaths reported in the active extension treatment study.

This figure provides a visual timeline of death relative to the last dose of study medication. The adverse events described for each subject was with the listed AE resulting in the fatal outcome of interest. Of the 9 deaths, six occurred after the last dose of the study drug and prior to 30 days of post-dose follow-up. While the incidence of death was unbalanced between the two groups, the overall incidence was relatively lower than that was observed in the 2005 FDA database. Based on the individual summary narratives, there was no clear pattern in the cause of death, and cases were often confounded by the underlying comorbidities, advanced age, and concomitant medications that are consistent with an AD patient population.

Based on the time frame of counting deaths that occurred within 30 days after the last dose of

study medication, the applicant estimated the incidence of death for the brexpiprazole group was 0.92 percent and 0.26 percent for the placebo group. In each of the phase 3 double-blind study protocols, the applicant indicated that the investigators would collect mortality status information by telephone at week 16 for all subjects who terminated early from the trial. All study completers and subjects who were withdrawn prematurely for any reason also underwent a safety evaluation 30 days after receiving the last dose of the study medication.

In our opinion, the review team believes that the applicant's sampling time frame to count deaths introduces the same bias that was previously discussed. In order to compare the findings from this program with the previous agency's meta-analysis and to limit this bias, a similar methodological approach was applied to estimate brexpiprazole's mortality risk in the AAD population.

Given the confidence in collected mortality status information at the 30-day safety follow-up period and at the week-16 mortality assessment, the

review team selected a sampling time frame of 114 days, which is equivalent to the intended period of observation of 12 weeks plus 30 days of the safety follow-up. This then provides an equal time frame to count deaths in both treatment groups.

Using the 114-day sampling time frame, the analysis included 7 deaths in the brexpiprazole-treated group and 1 death in the placebo group. In comparison with the applicant's finding, these counts only include one additional death in the brexpiprazole group.

The results of the mortality analysis demonstrated an incident-risk ratio of 4.16. Due to the small number of events in the program, there is great uncertainty in estimating the mortality risk as depicted by the wide confidence intervals shown in the forest plot on the right. The relatively low number of events in the placebo arm in this program, relative to the incidents observed from prior studies, included in the 2005 database, also adds to the uncertainty of the estimated mortality risk and may also be insufficient to characterize the

background rate of death in this population.

Although the mortality risk of brexpiprazole appears to follow a similar trend with other antipsychotics, the relatively few number of deaths cast additional uncertainty regarding the risk amongst the elderly patient population that will be prescribed the drug in the real world. Due to the evidence of the use of antipsychotics to treat psychosis and agitation results in higher mortality, we believe the boxed warning should remain to adequately inform healthcare providers, patients, and their caregivers.

In general, other safety findings were similar with the brexpiprazole known safety profile observed in patients with schizophrenia and major depressive disorder. The results of the active extension treatment study further suggested that continued treatment with brexpiprazole for up to 24 weeks did not reveal any new clinically meaningful safety signals.

In conclusion, there's a serious unmet medical need for the treatment of AAD. The applicant

appears to have provided substantial evidence of effectiveness for brexpiprazole for the use in AAD; however, brexpiprazole's mortality risk appears to be consistent with other antipsychotics in the elderly patients with dementia. With the available information regarding brexpiprazole's benefit-risk profile, we're looking forward to discuss brexpiprazole's clinical implications as a potential first-in-class product for the treatment of AAD.

That brings us to the questions for the committee, which we hope to guide our discussion later in the day. I want to thank you for your attention, and we'll now open for any clarifying questions. Thank you.

Clarifying Questions to FDA

DR. NARENDRAN: We will now take clarifying questions for the FDA. 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 again 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 a question with a thank you and end your follow-up question with, "That is all my questions," so we can move on to the next panel member.

Our first question is from Dr. Cudkowicz.

DR. CUDKOWICZ: Hi. Thank you for that really clear presentation. I don't know if you can answer this, but I was wondering your thoughts about that these particular deaths -- or 7 deaths -- are different from the ones you described in meta-analyses, the cardiovascular and infection, or maybe there's one infection in the placebo.

I was wondering what your are on that, and if you saw these other ranges in those meta-analyses. I'm struggling a little bit with how to interpret it since we're not seeing the same type of risks that are seen with the other antipsychotics.

DR. FARCHIONE: This is Tiffany Farchione,

just responding. I can pass this question to Dr. Stone. He also has a backup slide that he'd like to show related to this. But I think, just in general, one of the things that we can say about all of the deaths across all of the antipsychotic programs is that there is no unifying theme. We can't look at them and say like, "Okay. This is a unifying cause of death across all programs," or something that we can pinpoint to say this is how antipsychotics are causing death. We don't have that link. All we have is this association with a higher rate.

Dr. Stone, I can pass that to you for further clarification.

DR. STONE: Yes. Thank you. If you can see backup slide number 30, and put it up there, please.

DR. FARCHIONE: And please make sure to go on video when you're speaking.

DR. STONE: I think I'm on video.

DR. FARCHIONE: You are. I just didn't have enough boxes showing.

DR. STONE: Okay. Yes.

No, that's the presentation slide. We want backup slide 30.

This is the distribution of deaths, in red, death rates between drug and placebo for all the various causes of death that were identified in the meta-analysis, the red lines being confidence interval. So you can see they're across the board. Some are numerically larger but have pneumonia, but have a large confidence interval; others like sepsis are small and absolute terms, but have higher confidence intervals.

But it's also very difficult to describe the cause of death with a great deal of reliability and precision because this was a retrospective look at various reports. Also, it's quite common in clinical studies that the analyses are done on an unblinded basis, and the deaths that are associated with the study drug are looked at a lot more carefully than the deaths that are associated with placebo or even an active control, so there's also an element of reliability there.

But again, we see all sorts of causes of

death, and as Dr. Kalaria pointed out, it seems that what is occurring is that various health events are occurring, and their outcomes are worse in patients who were being treated with the antipsychotics. Maybe that's because when patients are calmer, they don't get as much attention and there's less recognition that something is going wrong, and that leads to a fatal outcome rather than one where the patient survives. That may also be very much the idea of calmness, where they're not being seen because they're not being agitated. It also may be that because they're calm, they're not going to make noise and they're not going to complain.

So it's a difficult issue but, again, I think it's a mistake to characterize the deaths as being something that the drug is doing directly to the patient. It's an interaction with the underlying morbidity, which is one reason why we perhaps saw so many fewer deaths.

In the brexpiprazole study, the average age was quite a bit younger -- it is age 74 -- and in these early studies, the average was 81, so we'd

expect to have a much lower background mortality rate, and the mortality rate for the brexpiprazole in this case was remarkably low, far less than you would have expected even for a cohort of people that age, and sex, and ethnicity, and nationality. We did that analysis, and the expected number of deaths in the placebo group, based on demographics, was 4 times greater than what was observed.

DR. CUDKOWICZ: Thank you. That's very helpful.

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

DR. PAGANONI: Thank you very much. This is Sabrina Paganoni. I have a question for the agency. Thank you for the clear presentation. The discussion points and the voting question have a lot to do with the overall benefit-risk assessment, and I noticed that on slide 37, you refer to your 2018 Type C guidance meeting, and the last bullet point states that the agency agrees that the long-term safety study would not be a pre-approval requirement but could be a phase 4 commitment.

So I was wondering, is this phase 4 commitment a consideration that we should consider as we discuss today, or no? If it's something that we should consider, can you tell us more about it?

DR. FARCHIONE: Any postmarketing requirements or commitments would be things that, obviously, we're going to discuss during our review process. If the committee feels like more safety information would be helpful in terms of clarifying the signal or anything along those lines, we would love to hear what kind of information you'd be interested in seeing, what sort of study design you think might be appropriate, and we can take that into consideration as we determine what we intend to put in the letter and what we might negotiate with the sponsor.

So certainly if that's something that you want to discuss as part of the Q&A session, I think that's a reasonable topic for the committee.

DR. PAGANONI: Thank you very much.

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

DR. IYENGAR: This is Satish Iyengar from the University of Pittsburgh. My question is about the modeling of the bias. At the end, did you get a numerical estimate of what the magnitude of the bias might be, or is the confidence interval for that so big that it's not that useful?

DR. FARCHIONE: I think that would be a question for Dr. Stone.

DR. STONE: The time frame was set up to avoid the bias, so it should be an unbiased assessment. As Dr. Kalaria pointed out, the way we analyze it, it added one additional death to the brexpiprazole group compared to what the applicant described, and that confidence interval is based on that unbiased assessment of the attention to observe for 114 days and our ability to observe both drug and placebo patients for 114 days and the rate of death within those 114-day periods. As Dr. Kalaria said, death is pretty unambiguous, and we are quite confident that all those deaths within the 114-day period were detected.

So that's an unbiased estimate, and just

because the numbers of deaths were so low, particularly among placebo, you have limited numbers, and that's why the confidence interval was wide.

DR. IYENGAR: Thank you.

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

DR. WEISMAN: Hi. Thank you. I had a question in that I'm struck by slide 559 that states that brexpiprazole's mortality risk is consistent with other antipsychotics used, but in a previous slide, CO-54, in the previous discussion we learned that it's actually really not consistent. It's much, much lower; it's much smaller, up to 4.5 percent treated with typical antipsychotics versus 1 percent with these studies, and that's a really important comparison, I think, because that's really the standard of care that's out there currently, along with a whole bunch of other medications in polypharmacy, as previously alluded.

Maybe I'm missing something in slide 559 about how it's consistent with other antipsychotics. Do you mean the relative risk between drug and

placebo? Thank you.

DR. STONE: Dr. Stone?

DR. STONE: Yes. It's the relative risk, and maybe if we could have backup slide 27, please?

As I said, the rate of mortality is low with brexpiprazole compared to the other antipsychotics, but it's much, much lower with this placebo group than compared to other antipsychotics. As you can see here, there's a difference in mean age of the population. The mortality rate observed on an annualized basis, brexpiprazole was a quarter of what we saw with the other antipsychotics, but the placebo rate was 10 times lower.

So the question is whether there was an unusually robust or healthy group of patients that may not be reflective of the target population. It may also be the case that it was just a statistical fluke, and that very few people died in the placebo group, as I said before, and the expectation, based on the age and sex and ethnicity and nationality, that the placebo death rate should have been 4 times what was observed.

At the bottom of the slide, there's another comparison where the observed mortality rate was what you would expect in a group of 59 year olds, not in a group of 74 year olds, so that's throwing the situation off. So either there's little increase in brexpiprazole based on what you'd expect to see for that demographic group, and there was something unusual, fluky, about the placebo group mortality being low, or that this was overall a very relatively healthy group of people for their age, and the mortality in the placebo group was reflecting that, and, in fact, the brexpiprazole group showed a higher rate of mortality. But again, the numbers are very, very small, so that's why we have wide confidence intervals, and you really can't say for sure.

DR. FARCHIONE: And I do want to just drive home the point that we're talking about the data observed in a clinical development program here, whereas the other data that we have that led to the boxed warning was a large meta-analysis based on both clinical trial data and also on postmarketing reports of deaths. So the numbers here are much smaller, the

confidence intervals are wider, so it really is difficult to compare. But the comparison we can make is that the signal is still there, it's still exists, and it appears to be relatively consistent when you take all of these different factors into consideration.

DR. STONE: Yes, just one small -up correction. The meta-analysis was based entirely on clinical trial.

DR. STONE: Based entirely on clinical -- okay. Thank you, Marc.

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

MS. WITCZAK: Hi. Kim Witczak. I think it's probably along the same lines that we just talked about. I know it was on page 34 of the briefing documents, but it was on your presentation, where it was 4.16 with the study drug, and then the overall meta-analysis. I can understand why we need the black box warning because it is still an antipsychotic, but have other companies -- because I'm still struggling with this idea of unmet need.

I mean, it's off label. We have real-world data? Do we have real-world data? I know this is the clinical analysis, but because it is, and a doctor can use it any way they want, is there any real-world data that we can actually look into that has been put into any of the MedWatch systems or any of that? Because, to me, this option is already been out there, so there's got to be some learning. And if that is double the risk compared to what's out there, I'm not sure it's the right thing. Then I know we've got issues with coverage because a lot of the nursing homes have come out and said they're not going to cover it.

So is this really about getting it covered; because it's now an official indication? So these are all things -- and maybe it's more of a discussion for this afternoon, but I'm wondering if you could just tell me if there is anything in the data that's already been reported through like a MedWatch system.

DR. FARCHIONE: Yes. We have very little postmarketing data for brexpiprazole in this population, so in terms of any FAERS reports or

anything like that, we have very little data.

From our pharmacovigilance team, do we have anybody who is able to chime in? Do we have anybody -- Dr. Vicky Chan, would you like to weigh in on this at all?

DR. CHAN: Yes. Hi. Vicky Chan, Division of Pharmacovigilance from the FDA.

In 2017, we completed a surveillance summary, which is an overview of the safety of brexpiprazole that included over 3,000 FAERS reports for brexpiprazole. Just as Dr. Farchione mentioned, we had very few reports of patients 65 and older. More recently, we did conduct a review to look at patients 65 and older to take a closer look to see if there were any reports of patients with this particular indication, and once again, we had very few reports; I want to say that about about five reports in patients 65 and older, so that's pretty much what we have. Thank you.

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

DR. THOMAS: Hello. Patrick Thomas, Baylor

College of Medicine.

Given the exclusionary criteria that were used in the applicant's studies, the exclusionary criteria -- if you can kind of summarize that -- was it that different in the meta-analysis? And if it was different, substantially, how would that affect your interpretation of real-world applicability in terms of mortality?

DR. FARCHIONE: Dr. Stone?

DR. STONE: Yes. Well, the most obvious difference is the difference in age. There may also have been some factors in terms of how patients were selected in terms of the definition of agitated Alzheimer's disease. These other studies, generally, the indication was dementia-related psychosis, and I think there's some question as to whether that's a real thing, but that's how things were considered; that these were people who were displaying some kind of psychotic symptom, which, of course, very agitated hostile behavior could possibly be a psychotic symptom, but were also perhaps more benign delusions and that sort of thing as well.

DR. THOMAS: I guess I was wondering more in terms of whether cardiovascular history of that was excluded, more so or less, in the studies that you looked at in the meta-analysis versus what would happen in the study.

DR. STONE: Right. Well, again, there were many different studies, but I don't think so because it was a targeted population, where the prevalence of these conditions is so high, it would be nearly impossible to conduct a study if you were tight in your exclusions.

DR. THOMAS: Thank you.

DR. NARENDRAN: So there's still a substantial amount of time? Are there any other questions to the agency?

Ms. Witczak?

MS. WITCZAK: Yes. I have a question. Has any other company ever come before you with this desire to get it approved for this application? I find it interesting that these products have been on the market that nobody else has ever come and tried to get this indication; and if they have, what were

the results? Obviously, it didn't pass because it's not there with that indication. And if they haven't, is there any kind of insight you could offer on that?

DR. STONE: Yes. We can't actually comment on any other development programs or anything that's under review. If you're interested in any publicly available information, I would recommend maybe checking clinicaltrials.gov to see what kind of trials have gone on, but we we can't comment on anything like that.

DR. NARENDRAN: I don't see any other raised hands. There's one more.

DR. CUDKOWICZ: Sorry. I don't know if this is a question you can answer, but just curious about what kind of options would there be, let's say, if it would be important to know the safety in people older than 80, at postmarketing, to collect that data in a way that would give meaningful results, given that there wouldn't be a placebo. I don't know all the regulatory options out there to do something like that. Is that something that you can discuss?

DR. FARCHIONE: Yes. There are a variety of

tools that we can use for monitoring and assessing postmarketing safety. I think what would be important for us to hear from the committee is where you think the holes are in the data, and then we can kind of explore internally which of our various tools would be appropriate. And if there is something that you think is important for us to know and we don't have a tool in our armamentarium in order to either request or require those studies, then that's also important for us to know. So I think that the better focus is on the type of information, and then on the regulatory side, we can figure out what we have.

DR. CUDKOWICZ: Okay. Thank you.

DR. NARENDRAN: Any other questions in from panel?

(No response.)

DR. NARENDRAN: I know we cut short a couple of people's questions for the sponsor. Do you have any questions for the sponsor before we decide to break?

(No response.)

DR. NARENDRAN: None? Okay. If that's all

we have, we could now break for lunch. It will be a little bit longer than what was planned. We will reconvene at 1:30 p.m. Eastern Standard Time.

Panel members, please remember that there should be no chatting or discussion of the meeting topics with other panel members during lunch. Additionally, you should plan to reconvene at around 1:20 p.m. to ensure you're connected before we reconvene at 1:30 p.m. Thank you.

(Whereupon, at 12:10 p.m., a lunch recess was taken, and the meeting resumed at 1:30 p.m.)

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

(1:30 p.m.)

Open Public Hearing

DR. NARENDRAN: We will now begin the open public hearing session.

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 applicant, its product, and if known, its direct competitors. For example, this financial information may include the applicant's payment of your travel, lodging, or other expenses in connection with your participation in the 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 this committee place great importance in the open public hearing process. The insights and comments provided can help the agency and this committee in their consideration of the issues before them.

That said, in many instances and for many topics, there will be a variety of opinions. One of our goals 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, please unmute and turn on your webcam. Will speaker number 1 begin and

introduce yourself? Please state your name and organization you are representing, for the record.

MR. KREMER: Thank you for the opportunity to offer comments. I'm Ian Kremer, executive director of the LEAD Coalition, the uniting voice of more than 200 member and allied organizations, working to improve quality of life for people facing Alzheimer's disease and related disorders while advancing the science to end dementia.

I have two disclosures. First, the sponsor and some of its competitors are LEAD Coalition member organizations; however, the vast majority of our members and allies are patient advocacy organizations. Second, I'm a member of the CMS Medicare Evidence Development and Coverage Advisory Committee.

Like many of you, I've known thousands of people with lived experience of Alzheimer's. Like many of you, my family repeatedly has been hit hard by dementia. The most recent loss was on December 24 when my beloved, brilliant father died after a long struggle with mixed dementia. We were

lucky because my father was spared the worst cruelties of agitation that my grandparents and so many others have suffered.

Non-pharmacological approaches to agitation work with some people and work in part for others. The IPA's agitation workgroup assessment and treatment algorithm rightly calls for these interventions to be tried first and thoroughly, but when non-pharmacological interventions prove insufficient, people living with agitation and their physicians should have meaningful access to FDA-approved, on-label pharmacological options.

The agitation experienced by millions of people is neither mild nor benign. For them, this is not a bit of fidgeting or an attempt to communicate a want or need such as pain management; this is agitation reflective of often extreme, unrelenting distress. Their agitation can be so intense and overwhelming that it causes self-harm and harm to others; caregiver retaliation; erosion of family bonds; premature institutionalization; and institutional care eviction. No one should

have to endure such symptoms that fundamentally undermine quality of life.

At a minimum, this agitation can be psychologically devastating. At its worst, this agitation can become life-threatening. Clinically, this would be called an increased risk of morbidity and mortality among people living with agitation and their families. We call it a living hell. For us, Dr. Atri's slide number 63, combined with the absence of sedation, is our North Star and our hope.

People living with Alzheimer's agitation, their families and doctors need options for on-label use of effective medications. Currently they have no FDA-approved, on-label medications to alleviate the symptoms and the psychological and physical harms. Today, you will help to determine whether their hopes, their urgent needs, will be met. The stakes for your deliberations and FDA's decision could not be higher for people whose lives are most profoundly affected by Alzheimer's disease. Thank you for your commitment to our

community.

DR. NARENDRAN: Thank you.

Speaker number 2, please unmute your mic and webcam. Please introduce yourself. State your name and organization, for the record.

DR. PATEL: I'm Ashok Patel. I'm an independent worker. I did geriatric psychiatry fellowship at Cornell, and I represent myself. My daughter is also geriatric faculty in New York City. I represent my patients mainly. I was trained in a nursing home, and I've been working there for 30 years now. I see these patients. I was there last in the past week. I was there for two days, and when I walked in, the nurse said, "Look at my scar. That patient with agitation did it."

We are dealing with 30 percent of these patients who have behavior problems in nursing. I work in nursing on a one-on-one basis. I have been teaching residents and geri fellows. I do research. I've done research with the sponsor, as well as other companies, looking at alternatives to

help these very, very difficult patients. In the current time, we do use numerous other methods to help. The nursing home does, by itself, all the other non-pharmacological methods. They're somewhat helpful, but not really that great, and we then end up using multiple combinations of benzodiazepines, atypical psychotics, and all that.

I have had experience with brexpiprazole. My own experience, particularly, is this is a patient who is a retired attorney. She was admitted because at home she could not recognize her husband. She would think he's an imposter. She called 911. She called the cops. She would beat up the husband, and all those behavior issues were happening that forced her to be in a nursing home.

Her son is an oncologist. He called me and said, "Doc, can you at least do something?" I said, "I have these programs. Let me see what I can do." We put her on the brexpiprazole program, and she was on open label. At the nursing home in the beginning, she would be in the dining room and

throw the whole plate to all these people around them. She would throw things. She would bite, hit, and scratch caregivers, so the caregivers thought, "Okay. Let's treat her in her own room." In her own room, she would be very belligerent, cursing, and screaming.

What happened then also is, these caregivers, when somebody is screaming and hitting them, they are also not that much interested in treating her. Her diapers don't get changed in time. She has --

DR. NARENDRAN: Speaker number 2, your time is almost up.

DR. PATEL: Okay.

So what I'm trying to say is with the brexpiprazole, we have seen much more benefit. We have continued to use it. We have no issues with any major side effects, and there's no discontinuation issues with the program. I appreciate your giving me a couple of minutes to talk about my experience in the nursing home. Thank you.

DR. NARENDRAN: Thank you.

Speaker number 3, please unmute your microphone and turn on your webcam. Please state your name and organization, for the record.

DR. ZELDES: Good afternoon. I'm Nina Zeldes, a health researcher at Public Citizen's Health Research Group. I have no financial conflicts of interest. I had slides.

Can you see my slides?

DR. NARENDRAN: We see them now.

DR. ZELDES: Perfect. Thank you so much.

Public Citizen strongly opposes FDA approval of brexpiprazole for the treatment of agitation in patients with Alzheimer's disease because, first, this drug's small benefit does not outweigh the significant risk and, second, due to the limitations of the provided data, a population for which the benefits outweigh the risks cannot be identified.

The evidence regarding efficacy is based on three studies of which only two reached statistical significance over placebo for the primary endpoint.

Moreover, in Study 283, statistical significance was only reached in the 2-milligram group. The treatment difference, on a score that ranges from 29 to 203 points, was minus 3.77, a result that FDA did not consider, quote, "statistically persuasive," unquote. Study 284 did not reach statistical significance. While the combined treatment difference of minus 5.32 in Study 213 was statistically significant, additional analysis, showed that for the secondary endpoint, only the 3-milligram group reached statistical significance. Based on these results, we disagree with the FDA's assessment that there is substantial evidence of effectiveness.

These limited benefits stand in opposition to serious safety concerns. For instance, common adverse events in subjects treated with this drug included urinary tract infections, somnolence, and insomnia. Subjects in the treatment arm generally also had higher incidence of adverse events of special interest, such as cardiovascular events. Of particular concern, however, is the almost

5 times higher mortality risk, a risk that FDA noted, quote, "follows a similar trend with the mortality risk estimated for other antipsychotics," end quote, as shown in figure 4 of the briefing materials.

Across all three studies, subjects were relatively young, had a low rate of co-morbid psychiatric symptoms, and were predominantly white. Based on the provided evidence, no patient group that would benefit from this drug was identified. Moreover, the dosing of this drug at 3 milligrams was only explored in one of the three studies.

In conclusion, there is not sufficient data to identify a population for whom the benefits outweigh the significant risks. Instead, like other antipsychotics, this is a drug that can kill patients without providing a meaningful benefit. We therefore urge the committee to vote no on the voting question, and strongly recommend that the FDA not approve this drug. Thank you for your time.

DR. NARENDRAN: Thank you.

Speaker number 4, please unmute your mic and turn on your webcam. Please introduce yourself and the name of your organization.

DR. TANN: Speaker number 4 is present. I was doing my level best to start my video camera. I'll give it one more try, and if it doesn't work, you won't see my face but you will surely hear my friendly voice.

Due to my activism and advocacy in the dementia space, I work with a multiplicity of orgs, but I am strictly speaking today with my voice and on my behalf. My name is Debra Tann. Allow me to speak to the specific affliction of agitation.

This neuropsychiatric symptom often wreaks havoc on persons living with Alzheimer's and their caregiving family. While there are no cookie-cutter medicinal answers for those suffering, brexpiprazole has revealed noteworthy clinical results. If these results offer a glimmer of family tranquility, that alone is worthy of this being a treatment option. So I say to you, if not now, then when? Thank you.

DR. NARENDRAN: Thank you.

Speaker number 5, please unmute your mic and turn on your webcam. Please introduce yourself and the name of your organization you're representing, for the record.

DR. SMALL: My name is Gary Small. I want to thank, first, the FDA for allowing me this time to speak with you today. I'm a geriatric psychiatrist, and I've been working with Alzheimer's patients and their families for four decades now. I've also conducted numerous research studies on the diagnosis and treatment of Alzheimer's disease. By way of disclosure, I consult with several pharmaceutical companies and other healthcare companies, including Otsuka, Lundbeck, and their competitors. But that doesn't impact my opinions today. I'm here to share my personal clinical perspective.

Let me start with the science by saying that I support this application. The clinical trial data are compelling. Based on my 40 years of experience as a clinical investigator, I find the

data on safety and efficacy reassuring and clinically relevant, and in this context, of a tremendous unmet need. Alzheimer's disease is a diagnosis with a horrible prognosis. Roughly half of Alzheimer's patients will develop agitation, the most troubling symptoms for patients and their caregivers.

I've known many family caregivers who are able to care for their loved ones that are suffering from moderately severe Alzheimer's disease; however, when the patient develops agitation, the burden becomes overwhelming. Primary caregivers of patients with dementia have a very high risk for developing depression themselves, and agitation in these patients further worsens caregiver stress. It accelerates the decline and quality of daily living for everyone involved and hastens patient placement into long-term care. We need help to keep patients in the community and delay long-term care placement, and this medication offers such assistance.

Currently, we have no medicine to treat this

common and troubling condition. I know how important it is to find new ways to help people with agitation due to Alzheimer's. We need to provide scientifically valid and humane ways to preserve family relationships and help patients remain in the community with their families for as long as possible. Given the compelling clinical data and great unmet need, I believe this compound is appropriate approval. Thank you.

DR. NARENDRAN: Thank you.

Speaker number 6, please unmute yourself and state your name and organization, for the record.

MS. VILLANIGRO-SANTIAGO: Yes. My name is Martha Villanigro-Santiago. Good afternoon, committee members. I have participated in focus groups and panels for several advocacy groups, including Otsuka, but I'm here testifying on my own behalf. Thank you for this opportunity to submit my comments as primary caregiver for my Latina mother living with Alzheimer's. I have witnessed her Alzheimer's accelerate with the untreatable agitation symptoms, which have caused a decline in

her physical and mental health.

When my mother was diagnosed with Alzheimer's 10 years ago, her primary doctor provided no information about the disease. During my mother's initial years with Alzheimer's, she did not rely on nursing homes. She was mobile and socially engaged with everyone. I consulted the psychiatrist. He explained that her negative expressions could be symptoms of Alzheimer's. He added that he could not prescribe anything to eliminate these symptoms; however, he could order medication to treat the mild mood swings. In fact, the temperament improved, and she enjoyed her days.

Unexpectedly, two years ago, her agitation symptoms increased. Both her symptoms and their frequency intensified. She began arguing with everyone. She refused to go to sleep, and she insisted on going home. In short, her daily enjoyment significantly declined. I tried to identify the non-medication route to address her agitation.

Like many other family caregivers, I began

to rely on a daily guessing game for identifying the best tool for maintaining my mother's quality of life. I thought I could easily identify situations or conversations that agitated her. This proved not to be as easy as I thought. I identified certain television shows that triggered my mother's anger and frustration. Her native language is Spanish; however, she could no longer watch these shows because it would make her angry and violent. After carefully selecting the TV channels, it didn't make a difference. They would also trigger anger.

Ultimately, I spoke with the psychiatrist. He suggested sedation or antipsychotic medication. He explained the latter would stabilize her mood and temperament but were not approved for Alzheimer's, but I saw a dramatic change in her behaviors after a combination of antipsychotic pills. She rested well. She no longer insisted on going home. Despite the warning on the label, the antipsychotic medication represented her enjoying her day with a smile.

In conclusion, as my mother's primary caregiver, I must learn and decide the best tools for maintaining her quality of life. Caregivers should not be forced to choose between ignoring a loved one's obvious challenges due to agitation or approving a not-approved medication to help a loved one with Alzheimer's. Thank you.

DR. NARENDRAN: Thank you.

Speaker number 7, if you could please unmute your mic and turn on your webcam. Please state your name and organization, for the record.

MS. PESCHIN: Sure. 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 sponsors and competitors for non-branded health education and advocacy on neuropsychiatric symptoms of dementia. Last night, the Alliance and the American Society for Consultant Pharmacists submitted a sign-on letter, asking all of you to consider the perspectives of people living with Alzheimer's and those who care for them as you discuss the proposed expansion of

the brexpiprazole label for agitation associated with Alzheimer's disease or AAD. We are joined by 31 partners, including the Caregiver Action Network; National Hispanic Medical Association; Us Against Alzheimer's; Voices of Alzheimer's; and many others.

It goes without saying, but I'm going to say it anyway, Alzheimer's by itself is a progressive and fatal disease. As you discuss the risks and benefits of brexpiprazole for AAD, please recognize this. A large longitudinal observational study published in the September 2013 issue of the American Journal of Psychiatry showed that it is the symptoms, not the use of antipsychotic medications, that predict nursing home admission and death.

One year ago, CMS announced that it would refuse to cover an entire class of FDA-approved, disease-modifying therapies for the treatment of MCI and early dementia due to AD. This effectively cut off access for beneficiaries living with early Alzheimer's, except wealthy seniors who could pay

out of pocket. It was a disheartening illustration of what happens when bureaucrats crunch numbers and forget about the people behind the math.

Currently, there is no FDA-approved medication for the unlabeled treatment of agitation associated with Alzheimer's disease. The published 2023 analysis of the safety, efficacy, and tolerability of brexpiprazole for Alzheimer's found statistically significant greater improvements in agitation versus placebo, supporting the findings of two prior clinical trials, and this sNDA follows eight years of accumulated safety and efficacy data on the original NDA. We were thrilled to see the FDA's comprehensive review, and we have full confidence in their recommendation to expand the label.

When I hear somebody speak about agitation as only needing to be managed with behavioral techniques, I wonder, has that person ever seen someone they care about repeatedly unable to stop restlessly rocking or pacing, screaming, or hitting themselves uncontrollably? If not, I would ask

them to think about what that might be like for the person experiencing it and for the caregiver trying their best to help.

The reality is that these symptoms often require medical attention. Providers are professionally trained to start with non-pharmacological approaches first, such as redirection or exercise; however, when symptoms progress, providers may need to recommend medication for the safety of both the patient and the caregiver, and that's truly the crux of benefit-risk care. Individuals living with Alzheimer's meet with their healthcare providers, often alongside family caregivers, to discuss the benefits and risks of whether to take a drug or not. Preserving a patient's dignity and well-being should be of the utmost importance. Thank you.

DR. NARENDRAN: Thank you.

Speaker number 8 has withdrawn, so speaker number 9, please unmute yourself and turn on your webcam. Please introduce yourself and any organization, for the record.

MR. PAULSEN: Thank you. Hi. I'm Russ Paulsen. I'm the chief operating officer of Us Against Alzheimer's. As a nonprofit, we are funded by private donations, and among those thousands of donors are Otsuka and its competitors. We're governed by a board of directors, which has no representation from any pharmaceutical company. I have no personal disclosures.

As a patient and caregiver-driven non-profit organization, we want to be sure that decisions affecting the lives of people living with this disease and their care partners are made based on an understanding of what matters to them, and we get that information, the understanding ourselves, by asking them what they think. Specifically, we have a cohort of about 10,000 patients and current and former caregivers, and from that cohort, we have both rich human stories and rigorous data.

Probably no one on this call, but many people think of Alzheimer's disease as being all about forgetting, or maybe forgetting plus a little confusion, but all of us who have ever cared for

someone with Alzheimer's knows it's so much more. Very few people decide that they can't take care of their spouse, or their parent, or their sibling at home anymore because that person forgets things or gets confused.

It's the neuropsychiatric symptoms. They show up in many people, and they just get worse and worse, and the stories are heartbreaking. You've heard many of them today. We hear them, too: a physician researcher -- until Alzheimer's came for him -- getting physically abusive for the first time; a grandmother who had been an artist suddenly deciding to use her cane as a weapon; a spouse losing sleep because his wife of six decades gets up in the middle of the night and starts pacing and cursing. It's scary stuff, and as the briefing documents and other speakers have noted, it's a reason that people end up in facilities, and they never get back home.

Quantitatively, our research team worked with researchers from Otsuka to assess the additional burden that caregivers of someone with

agitation face. This is quantitative research, finding that caregivers of people with agitation symptoms in Alzheimer's provided more hours of care. Fifty-two percent of them in the agitation cohort had to make one or more job-related decisions because of caregiving. That's about 12 percent higher in the agitation cohort, so 52 percent versus 40 percent. They retired earlier than they had planned. Their lives were upended, work impairment, absenteeism, more insomnia, more anxiety, more depression, and physical health symptoms as well.

As for the person living with the disease, when they have moments of lucidity and they become aware of what they've been doing, or what they've just done, they're devastated; and we know from our previous work, that being a burden on others is one of the biggest worries of people living with Alzheimer's.

Right now, as many have mentioned, doctors and families are having to manage this with very limited guidance, and we thank you, we thank the

researchers, the patients, and the caregivers who engaged in the trials that you discussed today. Thanks for taking this seriously, the problems and severity of the symptoms faced by our patients and their caregivers in evaluating this evidence.

DR. NARENDRAN: Thank you.

Speaker number 10, please unmute yourself and turn on your webcam. Please state your name and organization, for the record.

DR. MINTZER: My name is Jacob Mintzer. I'm a geriatric psychiatrist, staff physician of the Ralph H. Johnson Medical Care organization, and a professor at the Medical University of South Carolina; however, here I'm not representing any of these organizations. I'm only representing myself. I have received grant support, and I've been a consultant for Otsuka and its competitors; however, again, here I'm representing myself.

I've been treating patients with agitation in Alzheimer's disease for about 30 years. I've seen a loved one hitting the person that provides them care that is life-saving. I've seen the

caregivers having to be punished by the patient emotionally and physically, obviously, without intention, after providing care. I've seen the suffering of the patients when becoming aware of the problem also feel remorse and suffering, plus the suffering of the patient when they are agitated themselves.

I've seen, though, the doctors, when they try behavioral intervention and doesn't work, have the dilemma to either prescribe the medication that has a statement that it's not effective, and on top of that, has a black box that says they will have severe cardiovascular problems, and that will result to death.

I understand that there was a need to define a syndrome and to find effective and reliable measures to evaluate their effectiveness, and if those were met, then a medication could become available. I join my colleagues and the International Psychogeriatric Association in defining the syndrome first, and then definitely giving a final definition. Also, we validated the

instruments that were [indiscernible] statistically significant and will show meaningful clinical benefit.

Now, the question is, if a medication meets those requirements, are they going to be considered to benefit the patient? I am concerned that we may not give the patients, and the caregivers, and doctor the opportunity to, together, make the decision if this is the appropriate medication for patient.

Finally, I just have a thought. What would have happened if we would not have allowed patients to receive chemotherapy suffering from another fatal disease like cancer, and not have the opportunity to decide between them, and the patient, and the doctor to decide if that's the appropriate treatment for them? Alzheimer's disease is not less final, and we should consider it in the same light. Thank you for your time.

DR. NARENDRAN: Thank you.

Speaker number 11, please unmute yourself and turn on your webcam. Please introduce

yourself, for the record.

MR. TAYLOR: My name is Jim Taylor, and I'm the president and CEO of Voices of Alzheimer's. The mission of VoA is to empower people living with or at risk of Alzheimer's and other cognitive illnesses to drive equitable access to innovative care and treatment. In addition, I have previously served as an FDA appointed patient advocate, have participated in prior Alzheimer's ADCOMs, and would like to thank today's committee for serving in this capacity.

This is my terrific wife, Geri, who was diagnosed with Alzheimer's over 10 years ago. She participated in the aducanumab clinical trial for 7 years, so we are quite familiar with the research process. I'm not here to speak about research -- heaven knows there are many more qualified individuals to do that today -- but I know that there have been considerable advances in the last decade in atypical antipsychotic medications.

I'm here to speak on behalf of the people

living with Alzheimer's and their care partners, especially those patients in the moderate and severe stages of the disease who have the greatest degree of unmet needs. These treatments help control symptoms like agitation and aggressive behavior that can be distressing and even lead to injury of patients and care providers. For those who need treatment of this kind, their access is invaluable.

This new indication is particularly promising for people with Alzheimer's because it has been studied for them, and with your approval, will be the first treatment with label to reflect how it can be part of a care and treatment plan. The use of antipsychotic treatments in Alzheimer's has been extensively debated, but new research specifically on the benefits for Alzheimer's patients has led to changes in how these medications can be used effectively and with fewer side effects.

It's important that the FDA continue to embrace innovation for the care of people with

Alzheimer's since in the current environment, some payer bodies are using any manufactured controversy as a pretense to block patient access. It is critical that the FDA give full and unqualified support to drugs that have been developed to make the lives of people with Alzheimer's better. That is the only way that we can have access and continue to see progress in managing this challenging diagnosis. Thank you.

DR. NARENDRAN: Thank you.

Speaker number 12, please unmute yourself and state your name and organization, for the record.

MR. SCHREIBER: Yes. My name is Marty Schreiber, and I have lived with my wife Elaine for 20 years since her diagnosis. Of those 20 years, 12 were in the home with me and the eight were in assisted living memory care. Before we go any further, I want everyone to know how grateful we caregivers are for those of you that are working so hard to try and help our loved one live their best life possible. I'm not connected financially with

any of the outcomes of these discussions, other than to tell you that Alzheimer's cannot be cured or delayed, as we know, and therefore, what hope do we offer any caregiver or any person living with this disease other than to try and help them live their best life possible?

I believe that a medication that can get at that point is an extremely important benefit, not only to the person who suffers from Alzheimer's, but also to the caregiver because we know the impact of caregiving on caregivers, the impact on their health, their psychological well-being, the cost of medical expenses, and so on.

There's a caution, though, in that we have to make sure that any agitation is looked upon first as where is it coming from. Are there any physical surroundings or other aspects to this that bear in mind treating rather than going into a medication? Once we have understood that medication is the answer, it is certainly a godsend, a godsend to those living with Alzheimer's and a godsend to those as caregivers to help their

loved ones live their best life possible.

So it is my hope, then, that you take a good close look at this. It's my hope that should this agitation medication be proven effective, that we make sure that there's the proper guidelines to make sure that we outlaw any other kind of problem before the medications are given.

DR. NARENDRAN: Thank you.

Speaker number 13, please unmute yourself and state your name and organization, for the record.

MR. LEWIS: Hi. Thank you. This is James Lewis, speaking on behalf of the American Society of Consultant Pharmacists, and I want to especially thank the Psychopharmacological Drug Advisory Committee and the Peripheral and Central Nervous System Drug Advisory Committee for the opportunity to speak today. ASCP, the American Society of Consultant Pharmacists, does receive funding from a number of life science manufacture companies, including Otsuka and competitors, for non-branded health, education, and advocacy, with a focus on

older adults. At ASCP, we represent the pharmacists who are specialized in senior care, who work in a host of settings, including skilled nursing facilities, all the way through taking care of ambulatory community-based patients.

While there are many people who will speak today to the specific scientific merits, my comments will not be focused on that today; rather, I'm going to urge the committee to consider the perspective of the people living with Alzheimer's. Estimates vary, but there are at least up to potentially 6 million Americans over the age of 65 living with this disease, and as many more caregivers providing care to them.

As everyone is well aware, memory loss is not the only symptom of Alzheimer's. While that is the most common and recognizable symptom, it is not the only one. Many patients will experience a host of neurological and neuropsychiatric symptoms throughout the course of their disease, and these conditions and symptoms can lead to earlier death and earlier institutionalization.

According to the International Pharmacogenomics article, up to 70 percent of patients living with Alzheimer's disease will experience aggravation throughout the course of their disease, which this condition in particular has large impacts on the patient, the staff who are caring for them, and their family caregivers who are caring for them as well, and it's incredibly important that providers and caregivers have as many tools in the toolbox as possible to provide care.

While we can all agree that non-pharmacological approaches should always be tried first and other symptoms such as potential medication interactions be rolled out, it is imperative that we pursue the ability to have new medicines in our toolbox when they are clinically appropriate and clinically beneficial to the patient. As you are well aware, at present there is no FDA-approved medication for on-label treatment of aggression associated with Alzheimer's disease. There is a time that it is used off

label, but this can create real issues with reimbursement from insurance companies.

In particular, the issue before these advisory committees today is a supplemental drug application; it is not a new drug application. This medicine has been FDA approved since 2015, and there is an additional eight years of data on it that is supporting today's supplemental application, as well as this medicine has an encouraging safety profile in terms of dizziness, sedation, and deterioration of cognition.

With that said, I encourage the committee to look at this supplemental application with that in mind and the real need for providers, patients, and their caregivers to have options beyond simply what is existing now, which is, frankly, nothing. By putting more tools in the toolbox, we can provide better care to patients, extend their time with the most positive outcomes, and really limit, where possible, distress on the patient, their caregivers, and if it becomes necessary to institutionalize the patient, the institutional

staff.

As a family member who has had a family member with this disease, we've worked as hard as we could to keep this person in our home as long as possible to make sure that they were comfortable and getting the appropriate care, and thankfully for us, aggression was not one of her symptoms, but knowing other people who have, I know that that can be a real barrier to keeping people in the home safely for the patient and for the family who's taking care of them. So I encourage these advisory committees today to consider that in mind as you look at the more than 6 million Americans over the age of 65 living with this disease and their caregivers. Thank you again for your time.

DR. NARENDRAN: Thank you.

Speaker number 14, please unmute yourself, and state your name and organization, for the record.

MS. COMER: My name is Meryl Comer. I'm a founding board member of the nonprofit, Us Against Alzheimer's. My public comment offered to this

esteemed advisory committee is highly personal because I believe the caregiver is the keeper of the secret. For more than two decades, I cared for my husband and mother 24/7 in our home, and I can attest that each brain unravels in its own idiosyncratic way.

My husband, a physician and scientist at the NIH, was misdiagnosed for four years, in denial about his final Alzheimer's diagnosis. Any of life's minor inconveniences drove agitation, that if I couldn't redirect it quickly, it escalated and became more explosive. His doctor told me to call 911 if he got too dangerous. That was 24 years ago, and unfortunately nothing has changed. Tragically, there are no existing good options for treatments of dementia-related agitation, and the psychotic drugs now being used off-label have limited effectiveness and carry warnings for severe side effects.

The PRN given my husband by a night nurse at a major hospital to manage his agitation turned into an anxious man, because the rules wouldn't let

me stay with him, into a man barricaded in his room with a sofa blocking the door when I returned at 6:30 a.m. the next morning. After 2 months in the hospital, the final diagnosis, Alzheimer's with a behavior disorder and deemed too dangerous to come home. He was discharged with prescriptions for 16 Depakote and 4 Ativan a day. No facility would take him. I had to leave my job. I brought him home, and slowly weaned him off all of those medications. An agitated and dementing mind can harm anyone close by or weaponize even the most innocuous items in a home.

That said, all agitation should not be treated as equal. My 85-year-old mother, a former buttoned-up high school teacher at 5 five 2 [inches], acted out dementia totally out of character, biting and screaming profanities we were forbidden to utter as kids, and then crying because at some level she knew she was not herself.

Most all Alzheimer's caregivers who have reached out to me over the years share they avoid using medications unless absolutely necessary to be

able to keep a loved one comfortable at home instead of being institutionalized. Why? Because caregivers are the ones left to manage the side effects. Appropriate use guidance is critical to the decisions that we make.

In this committee's scientific deliberation on clinical meaningfulness, please consider the devastating impact of agitation across the spectrum of this disease. In closing, I believe that the FDA's integrity and scientific authority, that is the gold standard for this world, deserves our support and must not be undermined or overridden by the politics of our time. Thank you for your consideration.

DR. NARENDRAN: Thank you.

Speaker number 15, please unmute yourself and turn on your webcam. Please state your name and organization, for the record.

DR. ZUCKERMAN: Thank you. I'm Dr. Diana Zuckerman, president of the National Center for Health Research. My doctorate is in clinical psychology and postdoc in epidemiology and

biostatistics. Our non-profit think tank focuses on the safety and effectiveness of medical products, and we often work directly with patients. We do not accept funding from companies that make those products, so we have no conflicts of interest; however, my dad had dementia.

We all know that atypicals have a black box warning of death and also warnings about other serious side effects for dementia patients, and FDA says that Rexulti's, quote, "effect on mortality appears to be consistent with the known risk with other antipsychotics in elderly patients with dementia," and also, quote, "it's mechanism of action in the treatment of AAD is unclear," and that's a problem.

Looking at the CMAI total score -- sorry about that typo -- it's not significantly different for the low doses, and it's often statistically significant at 2-to-3 milligrams, but those differences are small, and there's no information after 12 weeks. Does efficacy improve or is it reduced over time? And even more important, the

CMAI has 29 questions about symptoms and should not have been evaluated by total scores. Self-harm kicking and screaming are much more disruptive than repetitive questions or repetitious mannerisms.

We need to know which specific behaviors were reduced compared to placebo. Table 14 on FDA's summary shows that most of these differences were not aggressive symptoms. Is it worth the increased risk of dying to reduce non-aggressive behaviors?

For the secondary endpoint, there weren't significant differences at 1 or 2 milligrams, and they were statistically significant for 2 -and-3 milligram groups when those were combined and, again, no information about whether efficacy improves or is reduced after 12 weeks. And even more important, why not measure quality of life instead of this scale? which measures overall mental illness.

Treating agitation is a seriously needed unmet need, but agitation is currently treated off label with other atypicals. So the question is, is

the safety or efficacy of Rexulti sufficiently superior to those off-label options to warrant FDA approval for agitation specifically for dementia patients, and is it appropriate to approve long-term treatment based on only 12 weeks of randomized-controlled data for a drug that can be fatal in the long-term?

In conclusion, patients deserve better, and many family members have told us that atypicals were a chemical straitjacket for their loved ones. Will family members be warned of all of the risks, and what are the rebound risks? Those haven't really been discussed. Since the risks of death are higher for Rexulti in the randomized trial compared to other antipsychotics that are not approved for dementia patients, don't we need larger, longer term studies before FDA approves Rexulti for dementia patients with agitation?

And my last point, many families tell us they were not fully informed of the risks of atypical; sometimes they were not informed at all. Realistically, if this drug is FDA approved for

dementia patients, it will be widely prescribed for dementia patients in nursing homes, and some of those patients will die unnecessarily as a result. Thank you for the opportunity to speak today, and I'm happy to answer any questions.

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 committee will now turn its attention to address the task at hand, the careful consideration of the data before the committee, as well as the public comments.

We have another 11 minutes. I was curious if any other panel members have any other clarifying questions for either the sponsor or the agency? We cut a couple people off during the sponsor's time. If you do have questions, please raise your hand to indicate that you have a question, and remember to put your hand down after you've asked your question. Please state your name for the record before you speak, and direct your question to a specific presenter, either the

sponsor or the agency. If you do have a question, as a gentle reminder, please say thank you or your questions are answered, so we can move on to the next panel member.

Any other questions pending?

(No response.)

Questions to the Committee and Discussion

DR. NARENDRAN: I do not see any questions.

If there are no further questions, the committee can now turn its attention to address the task at hand, the careful consideration of the data before the committee, as well as public comments.

We will now proceed with the questions to the committee and panel discussions. I would like to remind the public observers that while this meeting is open for public observation, public attendees may not participate, except at the specific request of the panel. After I read each question, we will pause for any questions or comments concerning its wording.

Question number 1 is a discussion question. Discuss the overall benefit/risk assessment of

brexpiprazole for the treatment of agitation associated with Alzheimer's dementia. In your discussion, take into consideration the following: the increased risk of death among elderly patients with dementia receiving antipsychotic treatment; the risks of medications that are often used off label for the treatment of agitation and dementia, example, antiepileptics, benzodiazepines, without established evidence of efficacy.

Are there any specific questions about the question, discussion question, from the panel members?

(No response.)

DR. NARENDRAN: It's pretty clear. If anybody wants to go first, please raise your hand, and we could start the discussion about what your thoughts are, anybody who has a formulated idea who wants to start. I see no hands.

Dr. Cudkowicz, thank you for going first.

DR. CUDKOWICZ: Thank you. Merit Cudkowicz. Actually, I don't have a formulated idea, but I have some discussion, and I wanted to start getting

other panel input.

I am pretty convinced about the benefit from these studies that are clinically relevant, as well as statistically sound, but there's more uncertainty about the risk around at least the deaths. I don't think the other adverse events are very -- they're manageable, but we just don't have enough data. There were, fortunately, only a small number of deaths in the study.

So I'm wondering, if this does become widely available, what type of data would be useful to collect? I think it's really about the older population to be able to have some assurance that the risk was not greater in that population compared to some of the current things that are being done off label. That's kind of where I'm kind of stuck, is how do we make sure that five years from now we have decent data on this older population who would start using this once it's on the market as an indication for Alzheimer's? So it's more of a question or further discussion for the panel, together.

DR. NARENDRAN: Thank you.

Dr. Apostolova?

DR. APOSTOLOVA: Yes. Hi. Thank you. Liana Apostolova, Indiana University. I am a dementia specialist, so I do encounter agitation daily in my clinic, and it is the most burdensome symptom of Alzheimer's disease, after psychosis, or right next to psychosis. Patients are desperate today and would like to get some respite, and what we do is we use off-label drugs. We use antipsychotics that have not demonstrated efficacy. Benzodiazepines, no, because they're not really very good drugs for this population; however, they're used wildly in nursing homes, causing problems. Antiepileptics we do use as well.

So, to me, having a drug that has demonstrated efficacy is really fulfilling a great unmet need. We don't have a drug like this to date. Yes, the class has increased risk of death, but we are already using other agents from this class off label in order to make these symptoms manageable for the families. Of course, patients

and families get counseled about the side effects and the risks involved, including the black box warning, and you know what? When we try to stop these medications families do not want to even attempt the titration down because of the symptomatic relief that they have seen in their loved one, in many, many cases.

I do appreciate the risks involved; however, it is up to the family -- usually these patients are far advanced -- to make risk-benefit decisions and participate mindfully in this discussion of treatment options, and benefits, and risks. That's all.

DR. NARENDRAN: Thank you.

Dr. Weisman?

DR. WEISMAN: I would totally agree with that. I think that was really well said, and I would also just add that we're talking a lot about the data surrounding mortality, but perhaps I'm not getting it because the absolute numbers are very tiny relative to historical previous studies. I know that there's an imbalance, and that's serious,

but upon my review of the inclusion and exclusion criteria, I didn't see anything that was that much different, other than the age, which I grant, but these people are very ill.

I think one thing that really caught my eye is that you have a dose response, so that's very clear, more drug, the better, but also you have a symptom response in which deeper symptoms are correlated with more improvement, like the worse it is, the better it can get. And I think that we see that with a lot of the symptomatic medications that we have, not just in our platform drugs for Alzheimer's disease, but also across psychiatry. So that was reassuring to me, that this drug has a lot of merit. Thank you.

DR. NARENDRAN: Thank you.

Dr. Fiedorowicz?

DR. FIEDOROWICZ: I can't start my video. It says because the host has stopped it. Can someone turn my video on, please?

Thanks.

Jess Fiedorowicz, University of Ottawa, just

talking about the risk and benefit, I appreciate everyone's input and all the data. The potential benefits from the data we saw seem quite clear, consistent, and as others mentioned, dose dependent, but it is small, probably about 0.3 standard deviations. It might even be smaller than what are minimally clinically important differences. There was a 2021 paper by the International Psychogeriatric Association suggesting that might be 5 to 17, but I think we can feel pretty confident, overall, that there is some potential benefit.

The risk is not super clear. In these small samples, the absolute risk was quite low, as the last speaker mentioned. The relative risk is high, but the estimates are really imprecise. So I don't know how we can really say that it's consistent with the prior when the confidence intervals could be consistent with no risk or an incredibly high risk.

So I think it's definitely very important for further study to better quantify that risk.

Ultimately, that risk decision is made in the clinical setting. In the open public hearing, we heard from speaker 7 discussing how caregivers, patients, and doctors need to discuss risks, and speaker 14, how all agitation should not be treated equal. Certainly there's a lot of context that needs to be considered in the risk-benefit decisions that's not going to be so easily made by some socio-demographic or clinical variables, so I think it's important for us to have information that providers, and the families, and patients that they're working with can use. Thank you much.

DR. NARENDRAN: Thank you.

Dr. Johnston?

MS. JOHNSTON: Thank you very much. I'm actually not a doctor, I'm a patient advocate, and I was a caregiver for my father for about 15 years, so all of this really hits home for me. But I also have a scientific side, and I have served on multiple IRBs and reviewed clinical trials for over 25 years.

Ultimately, with my father, when his

aggression came forward, he was in a care center, a memory care center, and I was a 3-and-a-half-hour drive over a mountain pass before I could get to him. I received a phone call that said I had three options. I could allow him to be arrested by the police, I could allow them to put him in an ambulance and admit him to a psychiatric ward, or I could get in the car and get there, and take him when I had nowhere to take him. I did not have an option of a drug that might help with his anxiety and improve his quality of life over his agitation. Ultimately, I had to choose to allow him to be sedated for him to return to the care center.

Unfortunately, as we've heard from other people, this dilemma has gone on for over 20-30 years of people not having an option. The scientific side of me would love more research on this, especially in the risk-benefit ratio, but in our older population, this does speak to their quality of life. It gives them a quality of life. He may not have gone into the downward spiral that he did by being sedated, which ultimately ended in

his death approximately 3 months later.

So I just feel like that even though the study sizes are small and there does need to be more information, I think as the patient advocate, which is what I'm serving as here today, for caregivers, this option is critical, and it's very important that we consider allowing that and allowing the clinicians to provide the family with the information they need so that the family can make the decisions. I think this is probably a jumping-off point for this type of treatment, and I know that there's more research out there, and I hope that we come up with even better solutions. But in the assessment of this, the advocate side of me says that we have to at least allow the option. Thank you.

DR. NARENDRAN: Thank you.

Dr. Paganoni?

DR. PAGANONI: Hi. This is Sabrina Paganoni. Thank you so much for the opportunity to review these data. I have to say this is a very important decision today. Clearly, it will affect

the lives of potentially millions of people, so I really appreciate all the input from the agency and everyone who spoke also during the public hearing.

I also appreciated the perspectives of our colleagues who are part of the panel today, who actually see patients with dementia and agitation, and I wanted to ask a few thoughts about how to monitor all of these, again, the population level moving forward. It's clear to me that the applicant has provided data that really provides some evidence of effectiveness, and clearly there is an unmet need; that's absolutely true.

Now, in terms of the individual decision and individual patient-doctor relationship, obviously, that's a discussion, and I appreciated the comments from previous panel members about the possibility of discussing risks and benefits on an individual basis; absolutely, that's clear. I'm also wondering, though, with respect to the question from Dr. Cudkowicz, as well as the comments earlier from members of the agency, in a different individual perspective, there is also a

responsibility towards the population when it comes to millions of people.

So potentially, also, I want to mention that if this drug were to be approved for the treatment of agitation in Alzheimer's disease, it's also possible that by extension or by off-label use, it could also be used for the treatment of agitation in other forms of dementia. Just like right now, we're using other drugs off label to treat agitation. It's possible if the drug was approved, it could then be used off-label to treat agitation in non-Alzheimer's forms of dementia.

So what I'm trying to say is that the use could really be substantial, and therefore, again, it does raise the question of how to monitor the safety in the broader population. I don't think this is a showstopper; I'm just posing that as a comment, and appreciate perspectives from the rest of the panel.

DR. NARENDRAN: Thank you.

Ms. Witczak?

MS. WITCZAK: Thanks for the opportunity.

After looking at the efficacy, I don't think the efficacy is there to outweigh the potential risk. Also, who were the people -- when we think about Alzheimer's and the progression, and people could live with it for many, many, many years because it does not have a curative effect on it, this potentially has the potential to be used for many, many years, or until death, or some of these other -- or withdrawal. We didn't hear a whole lot about the withdrawal.

In my opinion, right now it is still available for people to use off label, and it is being used off label. So the glimmer of hope -- because we know what will happen once it's marketed, and as the previous speaker just said -- it potentially can be used on a much wider range of people.

Those are some of my concerns. I don't think that the evidence that was presented, and especially the 2-point difference, and who were the original -- like were they severely agitated when they came in, or were they just at the beginning,

and we don't know how it progresses. In my opinion looking at studies, it was a small but also small duration, 12 weeks, and even when they looked at even 6 months; that when I hear some of the previous public speakers who talked about having loved ones that they cared for for 10-20 years.

So that is one of my concerns, and I would love to hear -- but again, I also go back to it already is available, and you can use it off label, or is this really more about getting it covered? Because we have all of the new concerns with EMS looking at what's going on in the nursing homes, and this would allow the nursing homes and whatnot to actually give a diagnosis and not have to look at it and put it under schizophrenia to get used for antipsychotics. So I'm just bringing those concerns up to the committee. Thank you.

DR. NARENDRAN: Thank you.

Dr. Baker?

DR. BAKER: Thank you, Dr. Narendran.

As an industry rep, I wanted to comment directly on the application that there are more

general issue that I've been thinking about as the committee's been discussing. I think this particular question, asking for a reference to the current state of care with off-label use I think calls for being conscious of what's known and what is unknown. We have heard comments through the course of the day, of course, that patients and their families -- or their families like continuing some of the off label use because they've seen the benefit, but likewise, this committee has carefully noted across many meetings in which I sat, the regression to the mean or placebo-treated patients are improving.

So that sort of anecdotal experience doesn't really measure up to actual clinical trials, so I think it's worth considering the benefit of what is established in terms of efficacy, as most of you have alluded to. You still weigh that against the risk, but I would just encourage being thoughtful that for the off-label use, it's much less certain whether there's any benefit at all where it's not been established, and likewise, even the risk of

deaths were somewhat imputing from what's established with antipsychotics, which mostly come from failed placebo-controlled trials for psychosis in Alzheimer's disease, which we haven't seen as much across the other classes, so thank you for that.

DR. NARENDRAN: Dr. Cudkowicz?

DR. CUDKOWICZ: Yes. I wanted to comment about the duration of treatment a little bit because, again, I don't see patients with this. From what I understood from the speakers we've heard from is that physicians would treat for short periods of time, like 3 months, and re-evaluate, and use, really, judgment with the patient and the caregiver about it. So I'm not really worried about this being a drug that people are going to take forever. It's really more that this is going to be a treatment option that's going to actually make a big difference for people and their families. I know we've talked a little about the effect size, but I am convinced that this is making a meaningful difference for people from the data

that we showed, particularly people who were more severe and had significant drops in parts of the scale.

I just wanted to address that because that came up as a worry, and I'm not sure we should worry about that part of it because I hope that physicians caring for these patients are going to use that judgment and standard approach of reassessing every couple months when people with Alzheimer's are on these type of medications. Thank you.

DR. NARENDRAN: Thank you.

Dr. Weisman?

DR. WEISMAN: Yes. I heard the concern about these folks not being sick, and I just wanted to push back about that because these people were were very sick. They were moderate to severe based on PI judgment in all the trials, from what I saw. I do these trials, and these are incredibly hard to enroll because there's a Goldilocks: if you're too mild, you don't get into the trial, and if you're too severe, it's impossible to bring them into a

clinic, and even in an assisted living facility, because these people should be on an inpatient psychiatric ward. So you're asking an impossible standard for these clinical trials because very severely agitated with basically homicidal behavior cannot be done in a clinical trial.

About the off-label considerations, off label is where we are now, so we're not doing the public health any service by saying, oh, we can't approve something just because it may be widened into other dimensions. That's really at the purview of the treating physician, one that should be wary of dementia with Lewy body, but I would see, really, no problem doing some people in frontotemporal [indiscernible] dementia. That's it for me. Thank you.

DR. NARENDRAN: Dr. Paganoni?

DR. PAGANONI: Hi. This is Sabrina Paganoni again. I agree with what many of the other people said, and I completely understand what Dr. Weisman was saying about the difficulty of enrolling in these trials and how sick the population is.

I also wanted to make a comment because earlier I asked the applicant about the effect size because, numerically, again, the delta between the two groups was relatively small. However, in looking at their primary endpoint and the exact questions that they asked and how they're scored, I was also reflecting on the fact that the person who scored -- actually, based on their criteria and the trial design -- had to be a caregiver or somebody at the institution and was with the participant at least, I believe, 2 hours a day for at least 4 times a week; so essentially not continuous monitoring.

So to me, it seems like the bar was very high. It's difficult to achieve these types of results. So I just wanted to make the point that my comment about effect size doesn't mean that I don't think there was a clinically meaningful result. I just wanted to understand it more, again, given the complexity of the population, the complexity of running trials in this population, and the fact that, again, the primary outcome, it's

hard to achieve significant changes on that just based on looking at the outcome -- I'm looking at that right now -- and the way the trial was designed. So in my mind, all of this speaks to a favorable benefit-risk profile.

DR. NARENDRAN: Dr. Thomas?

DR. THOMAS: Hi. Patrick Thomas. I do agree with several of the panel members that have mentioned that there is a clinical benefit, though small, consistent, and when you look at it several ways through minimally clinical important difference and mean, I think it stands up across looking at it several ways, despite the high placebo response, which one of the commenters noted; that that's something consistent across our psychiatric trials I think speaks to the endurance that there is a they're there, so to speak.

My kind of remaining question or concern is about not the safety profile, but that it seemed to be so much smaller in a younger population that had similar exclusion criteria. Now, that's not to say that, as other people have mentioned, that's reason

to not approve it, but unlike others who may say, "Oh, you know, a doctor will review it, and after 3 months, they'll reassess it," I think in the real world when you're out at your average nursing home, when you've got a doctor who's taking care of a panel of a hundred people in one spot, or a family's not involved, people are going to be on these medications longer than you think. So to really have an eye towards safety over time in an older population is going to be more reflective of what it may actually be, and would be important.

Again, I don't know that that's actually going to be above and beyond what's already out there because as other committee members have said, this is what we're already doing. There is a chance that it could be less harmful than the atypicals that we're already using, but there is a slight chance, given more time, that it could be more or equal, and I don't think that the data presented can let us really draw firm conclusions to that effect.

I would say that in comparison to some of

the things that are used off label, people kind of led with antiepileptics and benzodiazepines, which have clear drawbacks, but there's also -- while it's not maybe to this standard of evidence -- some evidence related to the use of your antidepressants, things like trazadone and citalopram. I think there was a head-to-head trial with citalopram versus Risperdal that showed benefit. Again, those things aren't being put forward for the FDA, and I don't know that this is necessary, but it certainly would be interesting to see if something in comparison with brexpiprazole and a medication like that would still clear that bar.

As it stands, given what's kind of the hand-waving idea of mechanism and how it might work, it seems to potentially hit a spot between an atypical and something like an SSRI or an SNRI, so I think think that there's some promise there. And given the level of unmet need, at this point, I kind of weigh towards that it's worth doing that and maybe having some caveats about extended

monitoring. That's all I have.

DR. NARENDRAN: Thank you.

From my standpoint -- this is Raj Narendran -- I agree with a majority of the panel members that this is a very difficult study to do, a very difficult population to enroll, and I'm pretty impressed that the company was able to demonstrate two trials' primary efficacy endpoint. The dose response was there. They enrolled a very sick population that included community participants, as well as a nursing home. So they did the best, and I feel like the efficacy overall is small but definitely is there. I kind of agree with that.

With respect to the risks, in terms of as an emergency crisis psychiatrist, ever since the black box warning went on, there's a reluctance to prescribe antipsychotics for elderly people, especially with dementia and agitation. Personally, I've felt like maybe we should get a geriatric psychiatrist to weigh in before we prescribe an antipsychotic.

So to have this data, and to know that it is no worse than the existing atypical, and maybe slightly better perhaps, we don't know for sure where it stands, but it's nice, and reassuring, and convincing to have some safety data well characterized, although it seems like there's a need for more. So that's where, personally, I come down.

Is there anybody else who wants to weigh in before we could summarize this question and move on to the next? Any other thoughts from the panel members about this?

(No response.)

DR. NARENDRAN: I don't see any raised hands, so in terms of the panel's consensus, I heard things that most people were convinced about the efficacy. I heard comments that people felt the effect was small but it was definitely there. People seemed to have come down heavily on the point that there was an effect, and the efficacy is not in question, although some people felt the small duration of the trial and the small effect

are deterrents in terms of a benefit. They would like that to be better characterized, but the majority of the people agreed on the efficacy.

In terms of the risks, what I heard was people felt it's hard to extrapolate from a 12-week trial. The short-term safety data, which very few people died, which is a good thing, but we don't know how this will reflect in the real world where patients will be prescribed this a lot more widely. Some people felt the black box warning, continuing with it would provide the opportunity to educate patients and families about the risks and the benefits; however, some people said maybe in the real-world setting, people may end up on these medications long-term, and risks could be higher.

I heard that the confidence interval is just too high to really say whether it's going to be less risky, or more risky, or is it about the same, so maybe there needs to be more data collected on its long-term safety and what it means in the real world. Also, I heard that people with other higher risks conditions like cerebrovascular disease and

stroke were excluded and may end up being prescribed this medication, and that could be a concern and increase mortality. However, I also heard that maybe that it shouldn't be a consideration for the risks, per se, because the indication is not necessarily for that.

So that's my thoughts. Anybody else want to weigh in? Did I miss anything or it's sufficient, and we could move on to question number 2?

(No response.)

DR. NARENDRAN: Question number 2, I'll read the question. Discuss whether there's a population of patients with Alzheimer's dementia for whom the benefit-risk of brexpiprazole appears acceptable. Is there a population for whom the benefit versus risk does not appear to be favorable?

Anybody have some initial thoughts? If you want to go first, Dr. Apostolova?

DR. APOSTOLOVA: Yes. Thank you. Liana Apostolova, Indiana University. The patients in whom the benefit-risk would not be favorable will be dosed with mild symptoms. We can use behavioral

approaches, caregiver training, family education, and all other non-medication approaches for addressing mild behaviors. Before starting antipsychotics, which do have increased risk of death, we always should make sure family education and caregiver training take place; however, in the severe cases, there is really no alternative. We go ahead and have to treat with an atypical antipsychotic; otherwise, the patient might get kicked out of the nursing home, and the family can't take care of the patient at home. It's a tragic situation in most cases.

So it would not be appropriate to treat patients with mild symptoms before education and caregiver training have taken place, but it is quite appropriate to discuss with the family the risks and benefits, and have them make a decision whether moving to an FDA-approved efficacious agent is what would be most beneficial.

DR. NARENDRAN: Thank you.

Dr. Paganoni?

DR. PAGANONI: Hi. This is Sabrina

Paganoni. I don't have much to add. I completely agree with everything that Dr. Apostolova said. It seems to me that this was a very well-planned clinical development program that showed consistent results across well-designed and conducted controlled trials. Obviously, when it comes to making clinical decisions in an individual patient, if symptoms are mild, as Dr. Apostolova said, there are other interventions that can be tried first, but then when it comes to patients with severe diseases, I don't think the data that has been presented today suggests that there is a specific subpopulation within that group that should not use this particular product if approved.

DR. NARENDRAN: Thank you.

Dr. Weisman?

DR. WEISMAN: I am also tempted to say moderate [indiscernible] would not be good, but also severe because very severe agitation didn't get into the trial, very likely, and also the separation was at 6 weeks. So if they're acutely and horribly agitated, severe would really not be a

great fit for this drug. I'd also say that I could see a mild person escalating, and I would definitely consider it, even though the symptoms were mild but failing more conservative management.

Then family preference, there are risk intolerant families and risk intolerant people, those who value quantity of life over quality perhaps, and maybe that would open up some doors to a personal discussion. But in terms of the risk, because there's no pattern in the deaths, I can't see that we can answer that in any satisfactory manner. Random is random. Thank you.

DR. NARENDRAN: Thank you.

Dr. Thomas?

DR. THOMAS: Hi. I'm Patrick Thomas. I essentially agree with what's been said before, potentially with mild and not in acute agitation because of the nature of the drug and the data that was put forth.

DR. NARENDRAN: Dr. Paganoni?

DR. PAGANONI: Thank you. This is Dr. Paganoni. I wanted to learn from the clinical

experience of my colleagues who have spoken, from their experience in dementia clinics.

Dr. Weisman, you mentioned that, again, there might be some groups where you may not consider this based on clinical presentation. I wanted to understand, if this drug is a symptomatic relief drug, do you expect the patient, the family, and the physician to really realize if there is symptomatic benefit in that particular patient over a relatively short period of time and adjust as needed based on that? Again, it's not a criticism. I just want to to better understand.

DR. WEISMAN: Yes. I do think if it works, and people are tolerating it well, then you'd want to leave it alone. I kind of agree with Dr. Thomas' previous point that this drug is very likely going to be a set-and-forget drug in the background, and that may have its own dangers because it hasn't been studied long term. But I would just put that out to the individual treating the person and discussing with the family.

Did I get that question right?

DR. PAGANONI: Yes. You also mentioned that there are people with very severe disease that perhaps would not be appropriate. I wanted to understand that as well.

DR. WEISMAN: Oh, yeah. I mean, I've had people turn on a dime who had a little bit of agitation. They wanted to leave, but all of a sudden they are agitated to the point of homicide; I mean, choking, stabbing. I called the police for somebody who is driving around the parking lot with reckless intent. We got to some of this before, but these stories, they just break your heart. This drug is not appropriate in somebody like that, who has to be institutionalized because if not, they are going to kill somebody.

DR. PAGANONI: Got it. Thank you. That's very helpful.

DR. WEISMAN: Thank you. I mean, animal torture, I have heard so many horrible things; setting fires. I mean, none of this stuff is captured, but it happens, and it is just off the hook. It's horrible.

DR. NARENDRAN: Panel members, does anybody else have thoughts, people who haven't weighed in?

(No response.)

DR. NARENDRAN: This is Raj Narendran. From my standpoint, I feel like we don't really have any data to pick one population or the other. I think the best would be to reflect what the clinical trial inclusion/exclusion was in the label, which is always done, and make people decide for themselves, and that's very hard to figure. Clearly, there seems to be in milder people, behavioral therapy is the standard, and probably should be, and in more moderate to severe, this medication seems to be effective. But I just don't have a clear sense, based on what we saw, that I could at least make those thoughts and recommendations for a subpopulation.

Dr. Thomas, go ahead.

DR. THOMAS: Given what was just brought up and what I kind of mentioned about, making sure that this isn't something that you're using in acute populations, is it to the point that in the

label, that would be something that would be a recommendation of the committee to consider? I don't know, but that's something I would put to my colleagues on the panel, if it needs that extra clarification.

DR. NARENDRAN: Dr. Iyengar?

DR. IYENGAR: This is Satish Iyengar from University of Pittsburgh. I have a question about the statement that this should not be used for the milder cases. I remember the down arrows, the improvement in symptomatology, as bigger, even for the milder cases. If there's no evidence of increased risk for the milder symptomatology, is it still your position -- I guess I'm talking to Dr. Weisman and I forgot her name -- that it's not recommended for the milder cases?

Apostolova, yes?

DR. APOSTOLOVA: Right. If I can then answer that since it was directed to me, and sorry if I'm jumping ahead of somebody else.

Yes, mild patients would not be indicated to have this as a first line of treatment.

DR. IYENGAR: I see.

DR. APOSTOLOVA: First, we have to try everything else that does not include medications, non-medication approaches, and many of those were outlined in the industry presentation. There is behavioral therapy, music therapy, and what-have-you, and there are multiple approaches. And based on what's available to a clinician locally at their institution, lots can be tried. Of course, family education is the most critical part. If that fails, then, of course, it would be indicated to start patients on treatment, and mild agitation was included in this trial, mild patients, mild cognitively impaired patients.

DR. IYENGAR: I understand. Thank you.

DR. NARENDRAN: I just want to provide -- Farchione or the agency to comment.

DR. FARCHIONE: Yes. I just wanted to follow up on Dr. Thomas' comment, and then some of the discussion about what sounds like people are concerned about PRN use as a possibility.

I just want to emphasize that that's not

something that's under consideration. In the clinical trials, people were administered the drug on a daily basis. That's the kind of dosage and administration instructions that the applicant is seeking in the labeling. I was worried that we might end up going off on a PRN tangent, so I just wanted to refocus.

DR. NARENDRAN: Thank you. That's a helpful clarification.

Dr. Cudkowicz?

DR. CUDKOWICZ: I don't think I was heading towards PRN. I was more talking -- there were comments about this is drop and forget, or this would be forever treatment, and my understanding of it is that's not how psychiatrists and neurologists work with their patients when they put them on these medicines; that they reassess the response rate at a certain interval, and either it's working and they'll continue it, or they'll wean it off a little bit with a minimum dose. So there was nothing that I heard that suggested that this was going to be a high-risk drug that you're going to

give, and you're going to forget about the person until something bad happens.

DR. NARENDRAN: Thank you.

Ms. Witczak?

MS. WITCZAK: Yes. I was going to just make a comment because of that drop and forget or set and forget, because that is in the real world. Again, I go back to the real world. Is that going to be what happens? And that is a big concern because that is what we're seeing. Whether it's at the nursing home and they have hundreds of patients or whether it's the family doctor that they go and see, that is one of my big, big concerns, is the set and forget, which is what we're seeing a lot with this.

Then I'm curious with the clinicians that actually see patients. Because this is already available to you as an off label, have you used it, and if you haven't, why not? And if you have, what were your results? Again, because it's already been out there as an option to be used off label, I'm curious if you use it, and if not, why not, and

so on. Thank you.

DR. NARENDRAN: Dr. Apostolova?

DR. APOSTOLOVA: Liana Apostolova, Indiana University. To answer the last question first, I have not used brexpiprazole. I have another agent that I commonly used, that I am prescribing to patients with good success. It's not one that is approved; it's off label, but it does relieve symptoms of agitation and psychosis.

To answer your first question next, many of us could potentially adopt a practice where we initiate a medication, provide 3-month refills, and then continuous refills after we assess, but that should be a physician's decision unless it's in the prescribing information, and if a practice like that can be recommended at certain intervals, that there is documentation of the continued need or something like that. Because I do agree with you that in real-world practice, once a medication is prescribed, sometimes it doesn't come off.

DR. NARENDRAN: I think we're going a little off track from the question and discussion. Just

to refocus back on the question, is there a population of patients for whom the benefit-risk of brexpiprazole appears acceptable? Is there a population for whom the benefit-risk does not appear to be favorable? I think we're kind of moving away. All of these are very important issues.

Dr. Weisman?

DR. WEISMAN: Well, yes, I think that's in the eye of the beholder. What could be mild-moderate for one family would be very severe and disruptive for another one. Right now, there is no standard of care, so there's this witch's brew of every medication, every intervention that you could imagine being used. Perhaps except neuroleptics, because of the scrutiny, they are underused, they are microdosed, and we see schizophrenia being overdiagnosed and improperly diagnosed, so right now, it's a mess. This is an unmet need. I guess that's not really to the question of whom would this benefit, but it would benefit agitated people, because the alternatives

are so bad.

DR. NARENDRAN: Just one second. I'm just waiting on some clarification.

Does any panel members have any other thoughts, people we haven't heard from?

Dr. Fiedorowicz, I didn't hear from you.

DR. FIEDOROWICZ: I don't have any additional comment.

DR. NARENDRAN: Thank you, Jess.

I see the sponsor wants to respond, so I'll give them an opportunity.

DR. ISMAIL: Hi. Dr. Ismail here. I'd like to respond directly to Ms. Witczak's comment about is this drug used, and is there experience with it. And I would like to inform the committee that I actually do have clinical experience with it, mostly over the last year with an N of about 30 patients.

Over this time period, it has basically supplanted all my other first-line choices when I need an antipsychotic, which is not unless the agitation is moderate to severe. It has become my

first-line agent for two reasons; number one, because it is not sedating; and number two, because it appears to work. And perhaps I'll add a third. The titration is really a lot easier than my previous first-line agent, which was aripiprazole, and it is much better tolerated than all the other antipsychotic agents with which we have experienced.

Some of my colleagues use very old drugs, which are much more dangerous, and as my practice evolves, right now, given the options, this is what I use first line, when I need an antipsychotic. Thank you.

DR. NARENDRAN: Thank you.

Any other panel members? I see Ms. Johnston.

MS. JOHNSTON: Yes. I just want to say -- and I may be oversimplifying -- in reference back to the question, is there a population -- we doubted that it does say there is a population that this would be acceptable for. Is there a population for whom the risk does not appear? I

don't know that we have enough data to say there's not, but there definitely is a population that it could be effective and seems to be effective for. So I don't know that we can answer the second part of that question clearly, but I think we can definitely answer the first part of it. That's all. Thank you.

DR. NARENDRAN: Thank you.

If there are no further comments, I will try to summarize what we've heard. In terms of what I've heard from multiple people in different ways was with mild behavior, perhaps behavioral therapy should be tried, and the more severe the agitation and the more moderate, brexpiprazole should be a reasonable option.

I also heard that there was probably not a clear discernible group that we could separate to say they did not benefit from it, although some people thought people with very, very severe acute agitation may not benefit from it, which is sort of veering into the PRN things, so we decided not to go there. But overall, it was not very clear, but

it is very clear that people who have moderate and severe agitation would probably benefit by this medication.

Any other thoughts that I didn't put in there?

(No response.)

DR. NARENDRAN: I guess not, so we will move to our voting question.

Dr. Joyce Frimpong will provide instructions for voting, and then I will read the question.

Joyce, it's up to you.

DR. FRIMPONG: Question 3 is a voting question. If you are not a voting participant, you'll be moved to a breakout room. Voting members will use the Zoom platform to submit their vote for this meeting. After the chairperson has read the voting question into the record and all questions and discussion regarding the wording of the question are complete, the chairperson will announce that voting will begin.

A voting display will appear where you can submit your vote. There will be no discussion

during the voting session. You should select the radio button that is the round circular button in the window that corresponds to your vote, yes, no, or abstain. Please note that once you click the submit button, you will not be able to change your vote. Once all voting members have selected their vote, I will announce that the vote is closed.

Please note that there will be a momentary pause as we tally the vote results and return non-voting members into the meeting room. 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 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 question, if any.

Are there any questions about the voting process before we begin?

(No response.)

DR. FRIMPONG: Since there are no questions,

I will hand it back to you, Dr. Narendran, to read question number 3.

DR. NARENDRAN: Thank you.

Question number 3, has the applicant provided sufficient data to allow identification of a population in whom the benefits of treating agitation associated with Alzheimer's dementia with brexpiprazole outweigh its risks? If you do not believe the applicant has provided sufficient data, what additional data is needed to support the use of brexpiprazole for the treatment of agitation associated with Alzheimer's dementia?

Are there any questions about the question? Panel members, if you do have any questions about the question, please raise your hands.

(No response.)

DR. NARENDRAN: Okay. It seems very clear.

If there are no questions or comments concerning the wording of the question, we will now begin voting on question number 3.

(Voting.)

DR. FRIMPONG: Voting has closed and is now

complete. After I read the vote results 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 question, if any.

There are 9 yeses and 1 no, and no abstentions.

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 provide justification of your vote, if you wish to.

We'll start with Dr. Thomas.

DR. THOMAS: Patrick Thomas, and I voted yes.

DR. NARENDRAN: Dr. Apostolova?

DR. APOSTOLOVA: Liana Apostolova. I also voted yes. I feel that brexpiprazole has demonstrated statistical significance and resulted in a clinically meaningful therapeutic effect, and

I'm convinced by the data.

DR. NARENDRAN: Dr. Cudkowicz?

DR. CUDKOWICZ: Merit Cudkowicz. I also voted yes, and I was convinced by the benefit and the unmet need, and also a reasonable safety profile. Thank you.

DR. NARENDRAN: Next is Dr. Iyengar.

DR. IYENGAR: This is Satish Iyengar from Pittsburgh. I also voted yes. I thought the studies were well done. The analysis was quite convincing. Generally speaking, I'm always a little bit leery of secondary analyses looking at severity, but in this particular case, I think what people know already from their experience matches the data, so thank you.

DR. NARENDRAN: Thank you.

Dr. Fiedorowicz?

DR. FIEDOROWICZ: Jess Fiedorowicz. I voted yes as well. As you may recall from my earlier comments, I did express concerns about the, either, width of the confidence intervals of the safety data, but we do have data from outside of these

studies as well while we wait for additional studies in this population that can be used, and I felt pretty heavily that the context of the clinical case needs to be considered in weighing the risks and benefits, and we wanted to have patients, families, and providers have that opportunity.

DR. NARENDRAN: Ms. Johnston?

MS. JOHNSTON: Yes. I voted yes. I feel confident with the safety, given this very difficult population, and I obviously feel like this is an unmet need that we've got to address, and I hope this is just the start of it.

DR. NARENDRAN: Dr. Paganoni?

DR. PAGANONI: Hi. This is Sabrina Paganoni. I voted yes. I think this was a well-planned clinical development program, and it provides prescribers with evidence-based data so that they can make informed discussions with their patients, so a good option to have.

DR. NARENDRAN: Dr. Weisman?

DR. WEISMAN: This is Dave Weisman. I voted

yes. I think the data speaks for itself. The efficacy data was positive and the safety data was very reassuring. That's it. Thank you.

DR. NARENDRAN: The next is me, Raj Narendran. I voted yes. I was very impressed with the sponsor's data as well. I thought the agency and the sponsor worked really well together to address a very, very difficult area, which there is such a great need. And given that there are no good options, I now feel like this data could be very helpful in informing providers, and families, and patients about the risks out there, so I kind of am convinced. I'm very glad to have seen the study being done, so I voted yes.

Ms. Witczak?

DR. WITCZAK: Kim Witczak, consumer rep. I voted no, and I've stated many of the reasons. But I don't think that the data demonstrated outweighs the dangers of an antipsychotic, which this is. Also, this is more for the FDA, but one thing for words of caution is when you start looking at the advertising, the marketing, and how it gets

communicated to the public, I think we need to really keep an eye on this. I do agree that it is an unmet need, and I hope I'm proven wrong in time. But with this limited amount, I'm not willing to vote yes for this product. Thank you.

DR. NARENDRAN: To summarize, 90 percent of the panel felt that the sponsor has provided sufficient data to identify a population in whom the benefits of treating agitation associated with Alzheimer's disease outweigh the risks. There was one panel member that had concern that still more data is needed to demonstrate that this is effective and safe.

If there are no other comments, before we adjourn, are there any last comments from the agency to the public or to the panel?

DR. FARCHIONE: Hi. Thanks, Dr. Narendran. No, I don't have any additional comments. I do want to just thank the committee for their thoughtful consideration, thank the sponsor for providing their comments today, and definitely thank the folks who participated in the open public

hearing session because, of course, that's really why we're here, is to try to find options for the folks who are experiencing these symptoms and their families, and hoping to address an unmet need, so thank you.

Adjournment

DR. NARENDRAN: Thank you. We will now adjourn the meeting. Thank you, everyone, and I want to thank the agency, the sponsor, and also everybody who participated in the open public hearing. Thank you.

(Whereupon, at 3:26 p.m., the meeting was adjourned.)