FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

PERIPHERAL AND CENTRAL NERVOUS SYSTEM DRUGS ADVISORY COMMITTEE (PCNS) MEETING

Virtual Meeting

Friday, June 9, 2023

10:00 a.m. to 4:34 p.m.

Meeting Roster

DESIGNATED FEDERAL OFFICER (Non-Voting)

Jessica Seo, PharmD, MPH

Division of Advisory Committee and

Consultant Management

Office of Executive Programs, CDER, FDA

PERIPHERAL AND CENTRAL NERVOUS SYSTEM DRUGS

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Robert C. Alexander, MD

(Acting Chairperson)

Chief Scientific Officer

Alzheimer's Prevention Initiative

Banner Alzheimer's Institute

Research Professor, Department of Psychiatry

University of Arizona College of Medicine - Phoenix

Phoenix, Arizona

Merit E. Cudkowicz, MD

Julieanne Dorn Professor of Neurology

Harvard Medical School

Chair, Department of Neurology

Director, Sean M. Healey & AMG Center for ALS

Massachusetts General Hospital

Boston, Massachusetts

PERIPHERAL AND CENTRAL NERVOUS SYSTEM DRUGS ADVISORY COMMITTEE MEMBER (Non-Voting)

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Assistant Director for Biostatistics

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Infectious Diseases

National Institutes of Health

Bethesda, Maryland

Colette Johnston

(Patient Representative)

Moab, Utah

Klaus Romero, MD, MS, FCP

Chief Science Officer

Critical Path Institute

Tucson, Arizona

Tanya Simuni, MD, FAAN

Professor of Neurology

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Northwestern University Feinberg School of Medicine

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DN1, ON, OND, CDER, FDA

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

(10:00 a.m.)

Call to Order

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

My name is Dr. Robert Alexander, and I will be chairing this meeting. I will now call the June 9, 2023 Peripheral and Central Nervous System Drugs Advisory Committee meeting to order. Dr. Jessica Seo is the designated federal officer for this meeting and will begin with introductions.

Introduction of Committee

DR. SEO: Good morning. My name is Jessica Seo, and I am the designated federal Officer of this meeting. When I call your name, please introduce yourself by stating your name and affiliation. We'll begin with the voting members of the committee, and start with Dr. Alexander.

DR. ALEXANDER: Good morning. Robert

Alexander from the Banner Alzheimer's Institute in Phoenix. Thank you.

DR. SEO: Thank you.

Next is Dr. Cudkowicz.

DR. CUDKOWICZ: Dr. Merit Cudkowicz from Mass General Hospital and Harvard Medical School, Boston, Massachusetts.

DR. SEO: Thank you.

Next, we have our non-voting committee member, Dr. Gold.

DR. GOLD: This Is Dr. Michael Gold, chief medical officer, Neumora Therapeutics.

DR. SEO: Thank you, Dr. Gold.

We'll now go to our temporary voting members and begin with Dr. Follmann.

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

DR. ALEXANDER: Thank you.

Next is Ms. Johnston.

MS. JOHNSTON: Yes. Good morning. My name is Colette Johnston. I'm a patient advocate, and I

work in the health physics department at a uranium towns help clean up here in Utah.

DR. SEO: Thank you.

Next is Dr. Romero.

DR. ROMERO: Yes. Good morning. Klaus Romero, chief science officer for Critical Path Institute in Tucson, Arizona.

DR. SEO: Thank you.

And Dr. Simuni.

DR. SIMUNI: Good morning. Dr. Tanya Simuni, neurologist, Northwestern University, Chicago.

DR. SEO: Thank you.

We'll now go to our FDA participants, and begin with Dr. Buracchio.

DR. BURACCHIO: Hello. Dr. Teresa Buracchio, acting director of the Office of Neuroscience in CDER at the FDA.

DR. SEO: Thank you.

Next is Dr. Jawidzik.

DR. JAWIDZIK: Hi. Good morning. Dr. Laura Jawidzik. I'm the acting deputy director of the

Division of Neurology 1 with the FDA. Thank you.

DR. SEO: Thank you.

And Dr. Yasuda.

DR. YASUDA: Good morning. I'm Sally Yasuda. I'm the deputy director for safety in the Division of Neurology 1 in CDER at FDA.

DR. SEO: Thank you all.

I'll return the floor to you, Dr. Alexander.

(No response.)

DR. SEO: Dr. Alexander, this is Jessica. You may still be muted.

DR. ALEXANDER: Sorry.

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

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

We are aware that members of the media are anxious to speak with 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. Seo will read the Conflict of Interest Statement for the meeting.

Conflict of Interest Statement

DR. SEO: Thank you, Dr. Alexander.

The Food and Drug Administration, or FDA, is convening today's meeting of the Peripheral and Central Nervous System Drugs Advisory Committee under the authority of the Federal Advisory Committee Act of 1972. With the exception of the

industry representative, all members and temporary voting members of the committee are special government employees or regular federal employees from other agencies and are subject to federal conflict of interest laws and regulations.

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

FDA has determined that members and temporary voting members of this committee are in compliance with federal ethics and conflict of interest laws. Under 18 U.S.C. Section 208, Congress has authorized FDA to grant waivers to special government employees and regular federal employees who have potential financial conflicts when it is determined that the FDA's need for a special government employee's services outweighs their 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 this 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 discussion of supplemental biologics license application 761269/s-001, for lecanemab solution, trade name Leqembi, for intravenous infusion submitted by Eisai, Incorporated, for the treatment of Alzheimer's disease initiated in patients with mild cognitive impairment or mild dementia stage of disease.

This product was approved under 21 CFR 314.500, subpart H, accelerated approval regulations, for the treatment of Alzheimer's disease. Confirmatory studies are studies to verify and describe the clinical benefit of a product after it receives accelerated approval. The committee will discuss the confirmatory study, BAN2401-G000-301, conducted to fulfill postmarketing requirement 4384-1 detailed in the January 6, 2023 approval letter. A link to this letter is available on FDA's website on the advisory committee meeting page, which can be found at www.fda.gov and searching for June 9, 2023 PCNS.

This is a particular matters meeting during which specific matters related to Eisai's supplemental BLA will be discussed. Based on the agenda for today's meeting and all financial interests reported by the committee members and temporary voting numbers, a conflict of interest waiver has been issued in accordance with 18 U.S.C. Section 208(b)(3) to Dr. Robert Alexander.

Dr. Alexander's waiver involves

stockholdings in competing firms. His waiver also involves his employer's research contract for one study funded by a competing firm. Dr. Alexander receives between $50,000 and $100,000 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 document, which is posted on FDA's website on the advisory committee meeting page, which can be found at www.fda.gov and searching for June 9, 2023 PCNS. Copies of the waiver may also be obtained by submitting a written request to the FDA's Freedom of Information Division at 5630 Fishers Lane, Room 1035 in Rockville, Maryland, 20857, or requests may be sent via fax to 301-827-9267.

To ensure transparency, we encourage all standing committee members and temporary voting members to disclose any public statements that they have made concerning the product at issue. With respect to FDA's invited industry representative,

we would like to disclose that Dr. Michael Gold is participating in this meeting as a non-voting industry representative, acting on behalf of regulated industry. Dr. Gold's role at this meeting is to represent industry in general and not any particular company. Dr. Gold is employed by Neumora Therapeutics.

We would like to remind members and temporary voting members that if the discussions involve any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement, and their exclusion will be noted for the record. FDA encourages all other participants to advise the committees of any financial relationships that they may have with the firm at issue.

Thank you, and I'll hand it back to you Dr. Alexander.

DR. ALEXANDER: We will now proceed with FDA introductory remarks from Dr. Teresa Buracchio.

FDA Introductory Remarks - Teresa Buracchio

DR. BURACCHIO: Thank you, Dr. Alexander.

I'd like to welcome our committee members and guests who are joining us today for this important meeting. At today's meeting, we will discuss the supplemental application for lecanemab for the treatment of Alzheimer's disease. You may have noticed that today's advisory committee is smaller than is typical.

In accordance with relevant laws and regulations ahead of any advisory committee meeting, FDA reviews the need for recusal of potential advisory committee members. For some topics like today's meeting, there can be a greater extent of recusals than for others. In particular, there was a recent submission to the docket for this meeting that included a large number of signatories, and that impacted our decision on the inclusion of several experts for this meeting who had otherwise been cleared to participate in this advisory committee.

Dr. David Weisman who was to serve with a

waiver, which was accordingly posted on our website in advance of this meeting, is one of the experts that was impacted by this submission. I would note that his other activities, publicly listed in the waiver, are consistent with our policies and procedures for serving on the committee with a waiver because his expertise and knowledge of this topic outweighs the potential for a conflict of interest created by the financial interests.

Today's smaller than usual committee reflects these challenges. While this group is small, it contains the appropriate expertise necessary to have a robust discussion on the topic at issue today.

I would now like to start the meeting by thanking the committee for the time that they have taken to review the advance materials and for joining us today to discuss the topics that are under consideration for this application. Your perspectives and input are very valuable to the agency.

I would also like to thank the public

attendees, and especially the patients with Alzheimer's disease and their family, friends, and caregivers who are joining us today. For those of you who will address the committee later today or have provided written comments for the committee, we look forward to and are deeply appreciative of your input and viewpoints.

Before describing some of the issues we will ask you to discuss today, I want to stress that we have not made any final decisions on the approvability of this supplemental application. Our comments in the background package are preliminary and do not yet take into account today's proceedings. Our presentations should not be viewed as necessarily indicative of our final decision. The reason we are here today is to gain your input into some of the challenging issues we have faced during our review process, so that we may incorporate it into our decision on approvability.

I will now provide some background on the development program for lecanemab and the issues

for discussion that bring us here today.

Lecanemab was approved under the accelerated approval pathway earlier this year on January 6th. The indication states that lecanemab is approved for the treatment of Alzheimer's disease and that treatment should be initiated in patients with mild cognitive impairment or mild dementia stage of disease. The indication also states that the accelerated approval was based on reduction in amyloid beta plaques observed in patients treated with lecanemab and that continued approval for this indication may be contingent upon verification of clinical benefit in a confirmatory trial. I will take a few minutes to explain the regulatory approval pathways and the basis for the lecanemab accelerated approval.

Traditional approval, also commonly referred to as full approval, is the usual approval pathway for most drug development programs. Traditional approval requires that substantial evidence of effectiveness be demonstrated on a clinically meaningful endpoint. This is often defined as an

endpoint that directly measures how a patient feels, functions, or survives.

A validated surrogate endpoint that has a strong and established evidence for its ability to predict clinical benefit may also support traditional approval. Examples of this include blood pressure reduction in cardiovascular disease and hemoglobin A1c in diabetes. For all approvals, the drug must be demonstrated to be safe for use under the conditions prescribed, recommended, or suggested in the proposed, labeling.

Accelerated approval is a particular type of approval that FDA may grant for a product intended to treat a serious or life-threatening disease or condition. The ability to use the accelerated approval pathway takes into account the unmet need in the disease such as the severity of the condition and the adequacy of available treatments or lack of available treatments.

Accelerated approval requires the demonstration of substantial evidence that the product has an effect on an endpoint that is not

itself a direct measure of the clinical benefit of interest, but is instead reasonably likely to predict that clinical benefit. Accelerated approval is subject to the requirement that the applicant study the drug further to verify and describe its clinical benefit.

The use of the accelerated approval pathway allows for the acceptance of some uncertainty with the use of a reasonably likely endpoint; however, it is crucial to recognize that the evidentiary standards for effectiveness are not lower for endpoints used to support accelerated approval than for traditional approval. Substantial evidence of effectiveness on those endpoints must be demonstrated.

Accelerated approval concerns the character of the endpoint. An effect on an endpoint supporting accelerated approval must be an effect on an endpoint that in its character is reasonably likely to predict clinical benefits, and in its persuasiveness provides substantial evidence of effectiveness from adequate and well-controlled

trials.

The agency considered these factors in determining that lecanemab met the criteria for accelerated approval. First, Alzheimer's disease is undoubtedly a serious and life-threatening disease. Although there are approved therapies for Alzheimer's disease, the course of the disease remains progressive and there continues to be an unmet need for effective therapies.

A phase 2 study demonstrated a robust and statistically significant reduction in amyloid plaque burden measured by positron emission tomography, or PET imaging, a surrogate endpoint that was determined to be reasonably likely to predict clinical benefit. These results were determined to meet the regulatory requirement for substantial evidence of effectiveness.

During the review of the initial lecanemab application, a phase 3, randomized-controlled clinical trial, Study 301, also known as CLARITY AD, was ongoing and completed, and was determined to be potentially capable of verifying

the clinical benefit of lecanemab for the treatment of Alzheimer's disease.

With the accelerated approval of lecanemab, a postmarketing requirement was issued for completion and submission of the study report for Study 301. That submission is the topic of our meeting today, whether the results of Study 301 verify the clinical benefit of lecanemab for the treatment of Alzheimer's disease.

Study 301 was a multicenter, randomized, double-blind, placebo-controlled, parallel group clinical trial. The study randomized 1,795 patients with mild cognitive impairment or mild dementia due to Alzheimer's disease to treatment for 18 months with either placebo or lecanemab. The study design and results will be discussed in much greater detail in the presentations to follow. I will just note that the study demonstrated statistically significant positive results on the primary and all secondary endpoints.

As lecanemab is already approved under the

accelerated approval pathway, the safety of lecanemab from the phase 2 study has been described in the approved prescribing information. The prescribing information has warnings for amyloid-related imaging abnormalities and infusion-related reaction. Amyloid-related imaging abnormalities, also referred to as ARIA, are imaging findings that may be observed on MRI and are associated with monoclonal antibodies that target amyloid. ARIA is typically categorized by findings of brain edema, referred to as ARIA-E, or as hemosiderin deposits resulting from microhemorrhages or superficial siderosis, referred to as ARIA-H.

The biological mechanisms that underlie ARIA are not yet fully understood, but it is hypothesized that ARIA may be related to vascular amyloid deposition and increased cerebrovascular permeability due to the clearance of amyloid beta. In the majority of cases, ARIA does not cause symptoms and is found incidentally on MRI; however, serious and life-threatening events can occur in

the setting of ARIA.

As we have an initial understanding of the safety of lecanemab from the accelerated approval, the safety presentation today will focus on the new data from Study 301, with an emphasis on ARIA and will consider whether any of the new data impacts our current understanding of the safety of lecanemab and the benefit-risk assessment.

Given these considerations, we seek the input from the advisory committee on whether the data from the phase 3 study verify the clinical benefit of lecanemab for the treatment of Alzheimer's disease, and ask the committee to discuss how the efficacy and safety data from Study 301 impact their overall benefit-risk assessment for lecanemab.

To this effect, the input that we receive from the committee today may differ slightly from other advisory committee meetings in which you may have participated or watched. In many advisory committee meetings, we are seeking input on the safety and effectiveness for the initial approval

of a drug or for a new indication for an already approved drug; however, in this situation, we are seeking input on the verification of clinical benefit for a drug that has already been approved, based on a reasonably likely surrogate endpoint.

This is also a drug with an identified safety risk of ARIA that is described in the current prescribing information. It is important to consider if the efficacy and safety data from Study 301 influence or change the established benefit-risk assessment for lecanemab for the treatment of Alzheimer's disease. The agency greatly values your input as we consider these issues in our review of this application.

Following my remarks, you will hear presentations from the applicant's team, and you will have a chance to ask clarifying questions. After a short break for lunch, we will reconvene with presentations from the FDA from Dr. Kevin Krudys, associate director for the Office of Neuroscience and clinical efficacy reviewer for this application; Dr. Tristan Massie, a reviewer

with the Office of Biostatistics; and Dr. Deniz Erten-Lyons, clinical safety reviewer from the Division of Neurology 1. I will then provide concluding comments on the presentations. You will, again, have a chance to ask clarifying questions. After a short break, we will have the open public hearing followed by a discussion. We will have a final short break followed by questions to the committee.

Again, no final decision has been made on approvability of this supplemental application and we very much look forward to the insights you will provide. We have convened this committee because we feel that a final decision requires your input and advice. Thank you for the efforts you have made in preparing for and attending this meeting, and thank you for the important work you will do today.

Dr. Alexander, thank you for the time to offer my comments, and I return the proceedings to you.

DR. ALEXANDER: Thank you, Dr. Buracchio.

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 a Eisai's presentation.

Applicant Presentation - Lynn Kramer

DR. KRAMER: Good morning. My name is Lynn Kramer, and I'm the chief clinical officer within the Alzheimer's Disease and Brain Health group at Eisai. I would like to thank the committee for your time today and the FDA for the invitation to review new and important data for lecanemab from Study 301, CLARITY AD. I also want to acknowledge the millions of patients with Alzheimer's disease who urgently need accessible treatments that can slow this relentlessly progressive, disabling, and fatal neurodegenerative disease.

As you can see on the left, we received approval based on our 856-patient phase 2B study. Today, we are pleased to share the lecanemab confirmatory study known as 301, which fulfills the requirements of conversion from accelerated approval to traditional approval. Study 301 demonstrated a consistent and persistent slowing of disease progression in patients with early

Alzheimer's disease.

Lecanemab is a treatment for patients with early Alzheimer's disease that selectively targets amyloid beta protofibrils. Our goal is to maintain patients in the earlier stages of Alzheimer's disease where they are most functional. In Study 301, lecanemab produced highly statistically significant and clinically meaningful slowing in multiple measures of clinical decline, accompanied by effects on biomarkers consistent with slowing of disease progression and decline of quality of life.

As the agency noted in their briefing document, Study 301 met all prespecified primary and key secondary endpoints with high statistical using validated measures of cognition, function, and amyloid reduction. The safety profile of lecanemab has been well characterized and is generally well tolerated, supporting a positive benefit-risk profile.

Known adverse reactions of ARIA-E and infusion-related reactions generally occurred early in treatment, supporting a focus period of clinical

monitoring early in treatment as described in the USPI. Importantly, Study 301 results are representative of U.S. patients with a broad range of comorbidities and concomitant medications from a diverse racial and ethnic background and across clinical practice settings.

First, let me share with you the agenda. Following my introduction, Dr. Michael Irizarry will present Study 301 efficacy results, then Dr. Shobha Dhadda will discuss the robustness of the data, and Dr. Irizarry will return to present safety. Dr. Sharon Cohen will provide a clinician's perspective, and I will return to conclude the presentation. Dr. Cohen has been compensated for her time and travel associated with this meeting.

Let me begin by providing some introductory remarks on Alzheimer's disease, lecanemab's mechanism of action, and regulatory history with the FDA. Alzheimer's disease has a complex clinical and biological continuum that begins 10 to 20 years before symptoms; 6 to 7 million Americans

65 years and older suffer from Alzheimer's disease, and it accounts for 60 to 80 percent of cases of dementia. Alzheimer's disease is ultimately fatal and is the sixth leading cause of death in the U.S.

Amyloid accumulation is the earliest detectable event, followed by tau hyperphosphorylation, together leading to synaptic and neuronal loss. This leads to impairments of cognition, daily function, and neuropsychiatric symptoms, which increase as the disease progresses. The complexity of care and cost burdens rise as the disease worsens, with severe impact on patients, families, and healthcare systems.

Importantly, there are no treatments that slow disease progression with traditional approval and broad access and established symptomatic treatments are insufficient. The currently established treatments -- cholinesterase inhibitors and glutamate modulators -- are symptomatic only, which means they do not impact pathophysiology or disease progression. These medications provide modest temporary benefit to symptoms, at best,

because the disease continues to progress, and no treatments are approved for mild cognitive impairment.

On this slide is a depiction of the amyloid pathway. Abeta dramatically and dynamically evolve through different species and molecular sizes. As shown, Abeta progresses across different conformational states, from soluble monomers to soluble aggregates of increasing size, moving from dimers, trimers, and oligomers to soluble aggregated protofibrils greater than 75 and less than 5,000 kilodal ton filaments. These progress to insoluble fibrils and amyloid plaques.

The red box identifies what are thought by many to be the neurotoxic forms important in driving progression of the disease and the downstream cascade. Lecanemab is a humanized immunoglobulin G1 monoclonal antibody that selectively binds most neurotoxic forms of soluble Abeta aggregate species. It has more than a thousand-fold selectivity for protofibrils over Abeta monomers and has low affinity for Abeta

monomers.

In addition, it has more than a 10-fold preferential activity for Abeta protofibrils over fibrils. The shaded line below the figure shows the relative binding profile of lecanemab, with the darker regions indicating the strongest binding with amyloid species. Lecanemab initiates microglial mediated clearance of protofibrils and plaques.

The lecanemab development program began in 2009 and included interactions with the FDA with alignment on the clinical development program. In 2021, lecanemab received both breakthrough therapy and fast-track designations. We also initiated a rolling BLA submission of Study 201 under the accelerated approval pathway, understanding the requirement for a study that confirms the clinical benefit and provides meaningful information. We obtained agreement from the FDA that Study 301 could satisfy that requirement.

In January 2023, lecanemab received accelerated approval for the treatment of

Alzheimer's disease in patients with mild cognitive impairment or mild dementia stage of disease. We submitted the results from Study 301 to the FDA the same day we received accelerated approval. The results of Study 301 confirmed the efficacy of lecanemab using globally established and validated measures of cognition and function in early AD and replicated the safety profile as reflected in the current USPI.

I would like to now turn it over to Dr. Irizarry to share with you these and other results from Study 301 in more detail.

Applicant Presentation - Michael Irizarry

DR. IRIZARRY: Thank you, Dr. Kramer.

My name is Michael Irizarry, and I'm the senior vice president and deputy chief clinical officer at Eisai. Study 301 was a multicenter, double-blind, phase 3 confirmatory study. It was a straightforward, two-arm study design at the currently approved dose of lecanemab 10 milligrams per kilogram intravenously every 2 weeks versus placebo.

The study enrolled patients with mild cognitive impairment or mild dementia due to Alzheimer's disease, with evidence of amyloid on positron emission tomography scan or by cerebrospinal fluid testing. All patients met NIA-AA diagnostic criteria, and the Wexler Memory Scale was used to confirm an episodic memory impairment.

Patients were randomized 1 to 1 to receive lecanemab or placebo for 18 months. Randomization was stratified by use of symptomatic Alzheimer's disease medications, AD stage, APOE4 carrier status, and region. Following the randomization phase, patients could continue in the ongoing open-label extension for up to 4 years.

Next, I'll review the outcome measures. The primary and key secondary endpoints were hierarchically tested. All endpoints were assessed as change from baseline at 18 months. The primary endpoint was the gold standard clinical outcome. The clinical dementia rating sum of boxes were CDR-SB. If the primary endpoint CDR-SB result at

18 months was significant, then key secondary endpoints were tested sequentially: the key secondary endpoints for amyloid PET change, the cognitive scale, ADAS-Cog14, the composite outcome ADCOMS, and the functional scale, ADCS MCI-ADL.

Study 301 also included three prespecified patient-reported outcomes to assess quality of life and care partner burden. Study 301 used validated and well-accepted AD clinical study endpoints to measure the change in cognition function as the primary and key secondary outcomes.

CDR-SB is a gold standard endpoint with 6 domains that assess cognition and function. Patients are scored from 0 to 18, with higher scores representing worsening disease. Most patients with early AD will have scores between 0.5 and 6. ADAS-Cog14 is also commonly used in clinical studies to assess cognitive change. Total scores from the 14 items range from 0 to 90, with higher scores representing worsening cognition. Most patients with early AD will have scores between 10 and 30.

ADCS MCI ADL is a commonly accepted endpoint to measure activities of daily living. The scale has 24 items of which 18 contribute to the total score, and these include assessments of the extent to which the patient performs home and community activities and whether they can be performed independently or with support. This scale ranges from 0 to 53, with lower scores representing worsening in functionality. Most patients with early AD will have scores between 35 and 45.

The ADCOMS endpoint is a scale not validated for longitudinal use but selected, as it is sensitive to detect early changes, and thus facilitated the Bayesian design of the phase 2 study. It was included in Study 301 to allow comparison to the primary endpoint of the phase 2 study. Since the Study 301 results align with the other more commonly accepted endpoints, ADCOMS is not discussed in detail in this presentation. All endpoints have been validated across multiple languages and regions, and they provide a comprehensive evaluation of disease progression.

1,795 patients were randomized and treated, 897 to placebo and 898 to lecanemab. Across groups, a similar proportion of patients discontinued from the study. Withdrawal of consent was the most common reason. Eighty-four percent in the placebo group and 81 percent in the lecanemab group completed the study, with data available for the primary endpoint.

Participants at baseline were generally similar across treatment groups. The mean age was 71 years and approximately 52 percent were female. For clinical diagnosis, approximately 60 percent had mild cognitive impairment and 40 percent had mild AD dementia. Global CDR scores and mini-mental state exam scores were well matched.

The APOE4 distribution reflected the general Alzheimer's disease population with 31 percent noncarriers, 53 percent heterozygous carriers, and approximately 15 percent homozygous carriers. APOE4 status is important because it is a risk factor for Alzheimer's disease and associated with an earlier age of onset. It is also associated

with cerebral amyloid angiopathy and increased risk of amyloid-related imaging abnormalities or ARIA. Additionally, just over half the participants were on cholinesterase inhibitors, or memantine, and so the study treatment was on top of these symptomatic treatments for Alzheimer's disease.

We also implemented efforts to increase the diversity in the clinical study population with regards to race and ethnicity, and also the range of comorbidities and concomitant medications to understand how the results generalize to the real-world early AD patients.

Shown here are the baseline characteristics for all patients in Study 301, shown in the middle column, and the 947 patients from the United States on the far right. Within the U.S., 5 percent of patients were black or African American and 22 percent were Hispanic, so the black population was underrepresented in the study and the Hispanic population was well represented. Although there were very few Asians in the U.S., the global study included substantial Asians, 17 percent overall.

Eligibility criteria allowed inclusion of patients with a broad range of comorbidities and concomitant medications. Over 50 percent of patients had hypertension or hyperlipidemia, 15 percent had ischemic heart disease or diabetes, and over half had multiple comorbidities. There was also an adequate distribution of common medications for this age group.

Baseline scores for each of the primary and secondary endpoints were consistent with the early AD population and balanced between treatment groups. Note that the baseline CDR-SB was 3.2, highlighting that the patients were on the low end of the CDR-SB scale. The mean baseline amyloid PET was approximately 75 centiloids. The centiloid scale is anchored at 0, which is the average in normal young controls which have no amyloid, and 100, which is the average in mild to moderate Alzheimer's disease.

Study 301, the confirmatory study, met the primary endpoint and all key secondary endpoints with a high degree of statistical significance.

Consistency in results was seen across all sensitivity analyses that Dr. Dhadda will describe later. Let me take you through each of these results graphically.

The primary endpoint was met in Study 301. Lecanemab significantly slowed disease progression by 27 percent on the CDR-SB at 18 months. Presented here is the adjusted mean change from baseline on the Y-axis and time on the X-axis. Clinical progression or worsening is represented by the downward arrow. Results were highly statistically significant with separation as early as 6 months. The treatment difference increased over time and was 0.45 at 18 months.

As a reminder, CDR-SB is based on patient and care partner interview, with six domains that assess cognition and function. In early AD, moving from 0 to 0.5 in a domain can represent a shift from unimpaired to impaired, and moving from 0.5 to 1 can mean moving from impaired to dependent.

Turning to the key secondary endpoints, lecanemab significantly reduced amyloid at all time

points from 3 months and beyond. Presented here is the adjusted mean change from baseline for amyloid PET using centiloids on the Y-axis and time on the X-axis. Less amyloid is represented by the downward trend. In the lecanemab group, there was an amyloid reduction of 55 centiloids at 18 months. Looking at the placebo group, amyloid increased by 4 centiloids. Additionally, results were highly statistically significant at all time points.

Presented here is the adjusted mean change from baseline for ADAS-Cog14 over time. As a reminder, ADAS-Cog14 is a cognitive test administered to the patient, assessing domains of memory, orientation, language, and learned motor function. Higher scores indicate greater impairment. In the confirmatory study, lecanemab significantly slowed disease progression by 26 percent on this cognitive scale. Results were statistically significant at all time points starting at 6 months. Similarly, lecanemab significantly slowed functional decline by 37 percent on the ADCS MCI ADL scale, with separation

as early as 6 months. Results were statistically significant at all time points.

Importantly, a 2-point difference was observed at 18 months. For context, a single point change can mean a shift for performing an activity unsupervised to requiring supervision or a shift from requiring supervision to requiring physical assistance by the care partner.

Turning now to biomarkers, Study 301 collected extensive biomarker data, providing the biological rationale for the observed clinical outcomes. Alzheimer's disease is characterized by early accumulation of amyloid, then the development of neurofibrillary tangles, neurodegeneration, and gliosis. Study 301 employed a comprehensive assessment of blood, cerebral spinal fluid, and imaging biomarkers of these processes. Let me briefly share results for three representative CSF biomarkers.

Lecanemab improved markers of amyloid with reduction of brain amyloid by PET in as early as 3 months and improvement is CSF Abeta-42, shown

here, as well as improvement in plasma Abeta-42/40 ratio. Biomarkers of tau showed improvement in CSF p-tau 181 shown here, as well as in plasma p-tau 181, and with slowing of tangle accumulation relative to placebo in the medial temporal regions by tau PET. For biomarkers of neurodegeneration and gliosis, there was improvement in CSF neurogranin, shown here, CSF total tau, and plasma GFAP. There were no significant differences in CSF or plasma NfL between lecanemab and placebo. Thus, through a comprehensive assessment of biomarkers, lecanemab impacted the underlying biology of Alzheimer's disease.

To further describe the consistency and robustness of the clinical outcomes, I will now turn the presentation over to Dr. Dhadda.

Applicant Presentation - Shobha Dhadda

DR. DHADDA: Thank you, Dr. Irizarry.

I'm Shobha Dhadda, senior vice president and global head of Biostatistics and Clinical Development Operations. My presentation will share the analysis demonstrating the robustness of the

primary analysis results. My presentation will show highly statistically significant results from all the analyses that demonstrate robustness of the primary analysis results. I will share how robustness was demonstrated using sensitivity analyses via various statistical methods to assess the impact of different assumptions on missing data. I will also describe the analysis performed to assess impact of intercurrent events such as discontinuations and use of symptomatic AD medications.

We also performed analysis to assess the impact of ARIA and infusion-related reactions. In addition, subgroup analysis by randomization strata were also performed. You will see that all analysis results are consistent with the primary analysis results.

At the top of each slide in yellow is the primary analysis for comparison. Shown here are the prespecified sensitivity analysis results that confirm the robustness of the primary endpoint results, using different methods compared to the

primary endpoint in the first row. These included assessment of the complete ITT population; rank ANCOVA performed with missing data imputed by multiple implantation; and the analyses on log-transformed data. As you can see, all are highly statistically significant with a consistent treatment effect. Log-transformed data demonstrated that the primary analysis results were not sensitive to departures from normality.

The prespecified tipping point analysis strongly reinforced the primary analysis results. Tipping point is a delta adjustment approach, which assesses how severe a departure from the missing at random assumption should be to overturn the conclusion of the primary analysis.

The results show that an implausible CDR-SB change among the dropouts would be required to tip interpretation. Look at the left figure. The X-axis is showing a shift of worsening to be added to the change from baseline on lecanemab dropouts; the Y-axis is p-value. You can see that the p-value is below 0.05 till worsening shift of 1.

We would need to assume that all dropouts on lecanemab worsened by an additional 1.5 points at 18 months on CDR-SB to make the results not significant. This means the dropouts on lecanemab needed to worsen by more than 2.7 points, which is a full point more than placebo group progression.

We need similar conclusions when conducting a tipping point for missing placebo patients on the right figure. These placebo dropout patients would need an improvement of about 1.5 points on change from baseline CDR-SB at 18 months to change the interpretation. This means that dropouts on placebo would need to have essentially no decline over 18 months on CDR-SB. Both of these cases are implausible and support the robustness of the primary analysis results, as was also noted by FDA in their briefing document.

Let us now look at the prespecified analysis accounting for intercurrent events, which also demonstrate the robustness of the primary endpoint results of Study 301 that are shown in yellow on the top row. For these analyses, we either censor

for initiation or dose adjustment of symptomatic AD medication, or treatment discontinuation in the middle row, or imputation by placebo results for discontinuations due to treatment-related adverse events. All analyses maintain highly statistically significant results.

Next, we evaluated the impact of potential unblinding due to ARIA, which was published in the New England Journal of Medicine and also infusion-related reactions. These analyses censor data after these events. As you can see from the results, all sensitivity analyses are highly statistically significant with results similar to primary analysis results.

Next, I'll present the clinical efficacy results by the four randomization strata. This study was randomized by the use of symptomatic AD medication at baseline, yes or no; clinical subgroup, MCI or mild AD; APOE4 status, carrier versus noncarrier; and region. CDR-SB results were consistent across subgroups. On this slide, you see a forest plot of the adjusted mean difference

and 95 percent confidence interval versus placebo by the full randomization strata. If you just scan down the center of the forest plot, you can see that all of the values are favorable to lecanemab.

This slide shows the forest plot for ADAS-Cog14, a key secondary endpoint. You again see that all of the values are favorable to lecanemab across all the randomization strata. Finally, here is the forest plot for ADCS MCI ADL, also a key secondary endpoint. Again, all the subgroups are favorable to lecanemab.

So in summary, lecanemab treatment met the primary and key secondary endpoints versus placebo, demonstrating results that were consistent with slowing of disease progression. Highly significant differences were achieved beginning at 6 months for primary and all key secondary endpoints that continued to widen and become more significant at 18 months.

Lecanemab showed clinically meaningful slowing of cognitive and functional decline. The results were consistent across endpoints and

subgroups, supporting the robustness of results, including sensitivity analyses. These results translated into slower decline in quality of life and care partner burden, as will be represented by Dr. Cohen at the end of our presentation. Lecanemab treatment resulted in significant reduction in amyloid plaques. Improvements in biomarkers of amyloid, tau, neurodegeneration and gliosis provided a biological basis for the treatment effects.

Thank you. I will now turn it back to Dr. Irizarry to present the safety data.

Applicant Presentation - Michael Irizarry

DR. IRIZARRY: Thank you, Dr. Dhadda.

Next, I'll discuss the safety results from Study 301 that demonstrate that lecanemab was generally well tolerated with a well-characterized safety profile that is consistent with the accelerated approval USPI, supporting a positive benefit-risk.

The mean duration of exposure was 15 to 16 months, and the majority of patients remained on

treatment through 18 months. Overall, 82 percent of patients treated with placebo and 89 percent of patients treated with lecanemab reported an adverse event during the 18-month double-blind study. Serious adverse events occurred in 11 percent of placebo and 14 percent of lecanemab-treated patients.

The known adverse events of special interest for amyloid-lowering monoclonal antibodies accounted for the imbalance relative to placebo in SAEs. The rates of SAE due to infusion-related reactions was 1.2 percent. The rates of SAE due to ARIA-E was 0.8 percent, and due to ARIA-H was 0.6 percent. Infrequently, ARIA can be serious and life-threatening.

AEs leading to discontinuation occurred in 3 percent versus 7 percent of participants on placebo and lecanemab, respectively. The differences in AEs leading to discontinuation are also due to the AEs of special interest. Deaths were comparable with seven on placebo and six on lecanemab. No lecanemab deaths in the double-blind

phase were considered by the investigators to be related to lecanemab or occurred with ARIA.

When looking across the most common adverse events, we see that the three most commonly reported AEs -- infusion-related reactions, ARIA-H, and ARIA-E -- are also the only AEs with important differences in rates from placebo. Notably, the ARIA rates are less than reported for other amyloid plaque therapies, and rates are consistent with the U.S. prescribing information for lecanemab. Other common adverse events have rates generally similar to the placebo group. There were no important changes in labs, ECG, or vitals, and there were no significant changes with these infusion-related reactions.

We observed a comparable safety profile across all lecanemab exposures in the core phase and the open-label extension phase for Study 301. Let's look more closely at the lecanemab adverse events of special interest: infusion-related reactions and amyloid-related imaging abnormalities or ARIA.

Ninety-six percent of infusion-related reactions were of lower grades of severity. Events typically consisted of flu-like symptoms. Seventy-five percent of the events occurred on the first dose. There were 7 patients among the 898 treated with lecanemab with grade 3 or 4 infusion-related reaction; 6 of the 7 events occurred with the first dose. Sixty-six percent of patients reporting an infusion-related reaction had only a single event. Overall, infusion-related reactions were manageable and generally self-limiting.

Moving on to amyloid-related imaging abnormalities, amyloid-related imaging abnormalities are identified by MRI and are usually asymptomatic. These are observed as either edema or hemosiderin deposition based on the MRI scan, and reported as ARIA-E or ARIA-H, respectively.

ARIA is a consequence of the presence of amyloid in cerebral blood vessels known as cerebral amyloid angiopathy or CAA. CAA is present pathologically in almost all Alzheimer's disease

cases, but most patients show no imaging findings such as microhemorrhage or superficial siderosis, or display clinical manifestations such as intracerebral hemorrhage or inflammatory CAA. CAA can cause spontaneous ARIA and intracerebral hemorrhage in patients with Alzheimer's disease. There is an increased risk of area with monoclonal antibodies that remove amyloid. There's a lack of definitive clinical criteria for diagnosing CAA in the absence of MRI evidence of hemosiderin.

The incidence of ARIA-E with lecanemab increased with number of APOE4 alleles, from 5.4 percent in noncarriers, 11 percent in heterozygous carriers, and 33 percent in homozygous carriers. ARIA-E events were largely mild to moderate radiographically in 91 percent of cases and asymptomatic in 78 percent of cases. The rate of symptomatic ARIA-E overall was 2.8 percent; 1.4 percent in noncarriers, 1.7 percent in heterozygous carriers, and 9.2 percent in homozygous carriers. When symptoms occurred with ARIA-E, the most common were headache, visual

disturbance, and confusion.

Among the 898 patients treated with lecanemab in the double-blind phase, there were 3 cases ARIA-E of severe clinical severity, which included symptoms of aphasia or seizure. Seventy percent of ARIA-E events occurred within the first 3 months of treatment and 90 percent occurred within the first 6 months regardless of APOE genotype.

Within Study 301, MRI monitoring was performed at screening, 9 weeks, 13 weeks, and 6, 12, and 18 months. The first follow-up MRI was prior to the fifth infusion. As shown here, the incidence of ARIA-E increases by number of APOE4 alleles, but the onset timing is similar across genotypes. These events resolve within 4 months of detection irrespective of APOE4 genotype.

Let's now look at ARIA-H. ARIA-H can occur with or without ARIA-E. ARIA-H that occurs without ARIA-E is known as isolated ARIA-H. Overall, ARIA-H occurs more frequently with lecanemab than placebo, and the incidence increases with the

number of APOE4 alleles. The excess ARIA-H with lecanemab relative to placebo appears to be driven by ARIA-H that is concurrent with ARIA-E on lecanemab, typically within the first 3 months of treatment.

Conversely, as shown here on the right, isolated ARIA-H is common with both placebo and lecanemab, and the incidence was generally similar in the two treatment groups. Isolated ARIA-H events occurred at a steady rate over 18 months of treatment in both the placebo and the lecanemab groups. Symptomatic ARIA-H tended to be associated with concurrent ARIA-E, with the most common symptom being dizziness.

In this analysis, the vast majority of ARIA-H events are microhemorrhages and superficial siderosis, often occurring in conjunction with ARIA-E. ARIA-E and ARIA-H events can be managed through periodic monitoring as recommended in the lecanemab USPI. The most consequential type of ARIA-H is intracerebral hemorrhage, and these are infrequent.

In this analysis, rates of ARIA are presented for patients who were not on an antithrombotic in the first row, those who were on an antiplatelet agent on the second row, and those who are on an anticoagulant in the third row. Comparing the rates of ARIA-E, ARIA-H, and intracerebral hemorrhage in adjacent rows, ARIA rates are higher in most categories for patients receiving lecanemab compared to those on placebo.

Looking down the columns, ARIA-E and ARIA-H rates do not appear to be higher in patients treated with lecanemab and a concurrent antiplatelet therapy or anticoagulant therapy, relative to lecanemab-treated patients not on these treatments. Because intracerebral hemorrhage has been observed in patients taking lecanemab, additional caution should be exercised when considering administration of antithrombotics or a thrombolytic. This is also stated in the current prescribing information for lecanemab.

In summary, lecanemab was generally well tolerated in an elderly early AD population with

many comorbidities and concomitant medications. The incidence and onset of ARIA and infusion-related reactions was consistent with the approved lecanemab USPI. These tended to occur early in treatment, supporting monitoring during the first 6 months of treatment. With the exception of ARIA and infusion-related reactions, the AE rates were comparable to placebo, supporting prolonged use of lecanemab.

Let me now ask Dr. Sharon Cohen to provide her clinical perspective.

Applicant Presentation - Sharon Cohen

DR. COHEN: Thank you, Dr. Irizarry.

I'm Dr. Sharon Cohen, a behavioral neurologist from Toronto Memory Program in Toronto, Canada. I have spent the past 30 years caring for patients with Alzheimer's disease at all stages of their illness, from the mildest to the most severe. I've devoted my career to improving outcomes for these patients and their families, as the disease they face is serious and devastating as it evolves. I've been an investigator in Alzheimer's clinical

trials over the same 30-year time span and have also been an advocate for individuals with various neurodegenerative diseases.

The objective of my presentation is to provide context to the clinical results in Study 301. I will do this first by sharing additional CDR analyses that speak to slowing of progression, namely a slope analysis using CDR sum of boxes and an analysis of time to worsening of global CDR score, and then by presenting health-related quality-of-life results from Study 301, which are prespecified exploratory endpoints. I will conclude with some reflections on what matters to patients and treating clinicians.

From the standpoint of the patient with Alzheimer's disease and the treating clinician, there are several urgent treatment needs. First, improving or maintaining core abilities of cognition, daily function, and behavior, each of which becomes severely impaired over the course of the disease; second, slowing disease progression

such that individuals remain at milder, less debilitating and less costly stages; and third, maintaining quality of life for both the patient and the care partner, given that Alzheimer's disease has an enormous detrimental impact on care partners, often multiple family members, in addition to its impact on patients themselves.

The benefit of slowing disease and of reducing decline in quality of life are highly stage dependent and are particularly relevant for the early stages of Alzheimer's disease, specifically the mild cognitive impairment and mild dementia stages when symptoms may be manageable and quality of life may still be good, but the specter of progression is real, and progression will lead to an intolerable state.

Patients and families frequently tell me that they can manage if things stay the way they are, but what they dread is getting worse, not recognizing their home or their spouse, becoming a burden to their children, or having to spend their remaining years in institutions.

Before I turn to the CDR analyses, let me clarify some of the points about what the CDR measures and what a change on CDR means for patients. The CDR is a scale of cognition and function that yields two different scores, a global score of disease severity and a sum of boxes score useful to discern change over time.

The CDR evaluates six domains, namely memory; orientation; judgment and problem-solving; community affairs; home and hobbies; and personal care. Each domain is scored as 0, no impairment; 0.5, questionable or slight impairment; 1, mild or unable to function independently; 2, moderate; and 3, severe impairment.

When the six domains scores are summed, the score ranges from 0 at best to 18 at worst; however, patients with mild cognitive impairment and mild dementia due to Alzheimer's disease typically have CDR sum of boxes scores between 0.5 and 6, not the full 18-point range. And importantly, moving from 0 to 0.5 in any one of the six domains means progressing from unimpaired to

impaired in that domain. Similarly, moving to a domain score of 1 means loss of independence in that domain.

It is generally accepted in peer-reviewed literature and amongst AD experts that a 20 to 30 percent slowing of disease progression is clinically meaningful. In keeping with this, a CDR-SB score change of 0.5 is commonly accepted as clinically meaningful in patients with early AD.

The CDR is a well-established tool, categorized as a global measure, as it incorporates perspectives of the expert clinician, the patient, and the care partner and assesses outcomes of cognition and function across multiple domains relevant to patients. The CDR-SB has the ability to demonstrate a clinically meaningful effect at the treatment group level. Furthermore, benefits may be expected to increase over time on the CDR-SB when a treatment substantially impacts underlying disease pathophysiology. Slowing of disease progression or time saved can also be demonstrated with the CDR-SB.

As you saw from Dr. Irizarry's presentation, the CDR-SB in Study 301 reduced clinical decline by 27 percent at 18 months, aligning with accepted meaningful delay in disease progression. Statistically significant separation from placebo was seen as early as 6 months, and the effect increased over the 18 months of the study. Additionally, all six domains of the CDR benefited from lecanemab treatment.

What you see here is a slope analysis which translates the group differences in CDR sum of boxes into measures of time saved or time preserved for patients. At 18 months, you see a 0.48 difference in CDR-SB between the lecanemab and placebo-treated groups such that the placebo group will have reached the level of progression that the lecanemab group reaches 5.3 months earlier than the lecanemab group. If we extrapolate the slope to 25.5 months, we now see a 0.68 difference between the two groups, translating into a 7.5-month delay in disease progression. In other words, with continued treatment, there is increasing time saved

by patients.

The ability of a patient to remain at an earlier stage of disease for a longer time is incredibly important in Alzheimer's disease. Disability can be captured in time-to-event analyses, which demonstrate delays in progression to landmark events. Landmark events at later stages of AD can include such milestones as institutionalization and death, while at early stages of disease, landmark events include loss of independence and a wide range of abilities that ultimately define who an individual is.

For patients with mild cognitive impairment who progresses to dementia, which is the next CDR global stage, that individual is no longer fully independent and perhaps can no longer work, or has to give up the car keys and/or hand over the banking, and may no longer be able to travel alone or live alone.

If you are a patient with mild AD dementia and you progress to moderate or even severe dementia, you have incurred even more substantial

losses of autonomy, requiring more and more supervision and care, and now we are no longer talking about whether you can drive or bank, but whether you can dress yourself, recognize your bed partner, use the toilet, find your way around your own home.

This slide displays an analysis of time to progression to more severe stages of AD using the CDR global score. The CDR global score stages individuals from 0 to 3 based on overall disease severity, with a global score of 0 being an unimpaired patient; 0.5 indicating mild cognitive impairment; and scores of 1, 2, and 3 representing mild, moderate, and severe dementia.

From the analyses depicted, lecanemab reduces the relative risk of patients progressing to the next CDR global stage of disease by 31 percent, corresponding to a hazard ratio of 0.69, even within the 18-month time course of the study, thereby allowing individuals to remain in earlier, less disabling stages of AD for longer periods of time. Again, progression to the next

CDR global stage is not trivial in this disease, and reduced risk of progression is extremely important to patients and their care partners.

Turning now to health-related quality of life, let's take a moment to understand what this means. Health-related quality of life can be defined as one's perception of how one's well-being is affected by a disease, disability, or a disorder. This is not interchangeable with health status, and it is a broader construct than activities of daily living but often correlates with measures of function due to the high value that individuals place on their independence.

Health-related quality-of-life measures are ideally rated by patients themselves, and rated in relation to their own personal expectations, which can vary over time and with disease. This is particularly important in early stages of AD when patients are more insightful about their experiences and abilities, and their care partners are less able to discern some of the subtle but important changes that the patient's themselves

notice.

Health-related quality-of-life questionnaires may be multidimensional, covering physical, social, emotional, cognitive, work or role-related aspects, and/or more disease specific related to such aspects as relevant symptoms, side effects, and financial impact of the disease. Health-related quality-of-life measures provide patient-reported outcomes, which are central to our understanding of the value of the treatment.

Here are the three health-related quality-of-life scales employed as prespecified exploratory outcomes in Study 301. Of note, each assessment was performed at baseline and every 6 months thereafter. The first scale in the table, the European Quality of Life Five Dimensions Five Levels, is a commonly used general health-related quality-of-life scale, which is rated by the patient.

The EQ-5D-5L asks patients to assess their health on the five dimensions of mobility; self-care; usual activities; pain and discomfort;

anxiety and depression. The measurement uses a visual analog scale from 0, worse imaginable health, to 100, best imaginable health. Being a general health-related quality-of-life scale, not all dimensions are equally relevant to Alzheimer's disease. Specifically, pain is not a part of Alzheimer's disease and mobility is not relevant in early AD.

The next scale, Quality of Life in AD, or QOL-AD, is a 13-item questionnaire which obtains input from patients on their quality of life related to the disease. Questions probed include one's satisfaction with one's ability to do things, satisfaction with one's living situation, with one's relationship, with friends and with family, and with life as a whole. The score range is 13 to 52.

The Zarit Burden Interview is an AD-specific, 22-item instrument used to assess care partner burden associated with Alzheimer's disease, including the psychological, emotional, financial, and physical aspects of providing care.

Importantly, it is rated by the care partner on behalf of the care partner. The total score is 0 to 88, with 0 to 21 reflecting no to mild burden; 21 to 40, mild to moderate burden; 41 to 60, moderate to severe burden; and greater than 61, severe burden.

I'd like to emphasize that in MCI and mild AD, the patient is the best source of reporting regarding the impact of the disease on themselves, while the care partners are the most important appropriate individuals to rate the impact of the burden they experience.

Here you see the results of the EQ-5D-5L rated by the patient. At baseline, we see that the scores are well balanced between placebo and lecanemab groups, with a mean score of approximately 82 on a scale where 100 is the best imaginable health and zero the worst imaginable. These baseline scores reflect a mild state of impact of Alzheimer's disease.

At 18 months, there was a highly statistically significant difference between

placebo and lecanemab-treated patients of 49 percent less decline in health-related quality of life, with an adjusted mean treatment difference of 2 and a p-value of 0.00383. In addition, the three dimensions that were most relevant to early AD benefited most from lecanemab, namely, mood, self-care, and usual activities. Furthermore, the benefit on these relevant domains is seen across all four randomization strata, including disease stage; APOE carrier or noncarrier status or APOE4; background AD medications; and geographic region.

Turning to the patient-rated QOL-AD, baseline scores are, again, well balanced between treatment groups, with the baseline score of 39 corresponding to good quality of life on this scale, from 13 to 52, which spans poor, fair, good, and excellent. And therefore, baseline scores, again, reflect mild impact of quality of life in this early AD cohort.

For QOL-AD, there was 56 percent less decline in patient quality of life at 18 months, with an adjusted mean treatment difference of 0.66

at a p-value of 0.00231. The item level analysis at this AD-specific scale shows that lecanemab was evident on virtually all of the 13 items, ranging from less decline in functional abilities to less decline in relationship, mood, finances, and life as a whole. Benefit was also seen consistently across randomization strata.

Turning now to the care partner on the ZBI, the baseline score is approximately 17, which corresponds to no to mild burden on this scale, which ranges from 0 to 88. Importantly, this reflects that in early AD, care partner burden is minimal, and that is exactly where we want it to stay. At 18 months, care partner burden was reduced by 38 percent relative to placebo, with divergence from placebo being seen already and highly statistically significant at 6 months, and the benefit increased over time.

The item level analysis for the ZBI shows lecanemab benefit across all items on this scale, which includes common caregiver concerns such as not having enough time; not having enough money or

privacy; feeling one's social life has suffered; feeling embarrassed by one's loved one; and having lost control of one's life, to name a few. Furthermore, lecanemab benefit on the ZBI was seen across all randomization strata.

Allow me now to share a few reflections on what these lecanemab results mean to treating clinicians. First, clinicians value consistent data across multiple key aspects of the disease they are treating. The consistent benefit of lecanemab across multiple measures of cognition, function, biomarkers, and health-related quality of life is striking, with 26 to 37 percent less decline on clinical outcomes and up to 56 percent less decline on quality-of-life measures.

Collectively, these results provide clinicians with clear rationale for lecanemab treatment in early AD, and moreover, provide the clinician the opportunity to intervene early, even in the pre-dementia MCI stage of the disease where we have not previously had treatment options; and what this means is that the clinician no longer has

to stand by, wait, and watch their patient deteriorate before treatment can be initiated.

Second, patients and clinicians value disease slowing when dealing with what is otherwise a relentlessly progressive, severely disabling disease. Here again, Study 301 provides clear evidence of slowing of decline through multiple analyses on multiple clinical endpoints, thereby providing reasonable assurance to clinicians that the patients in front of them will benefit in meaningful ways.

Third, diverse study populations with respect to broader age range than usually included in AD clinical trials, broad background medications, comorbidities, race and ethnicity provide treating physicians with confidence that study results are applicable to their patients in their real-world practices.

Finally, health-related quality-of-life measures are rarely reported in AD clinical trials, and positive health-related quality-of-life results over multiple scales provide patient centricity

that is paramount to clinicians, as it is the clinician's obligation to meet the needs of patients and to be responsive to what actually matters to their patients.

Thank you. I'll now turn the presentation back to Dr. Kramer to conclude.

Applicant Presentation - Lynn Kramer

DR. KRAMER: Thank you, Dr. Cohen.

In summary, Study 301 confirms consistent and persistent clinical benefits in patients with early Alzheimer's disease and fulfills the requirements for traditional approval. The data presented today support that lecanemab is a clinically meaningful treatment that slows disease progression.

Lecanemab produced highly statistically significant results that demonstrated an important slowing in cognitive decline, functional impairment, and a positive impact on quality of life for patients and their caregivers. The two adverse events of interest, infusion-related reactions and ARIA, have been well characterized

and can be effectively managed with early monitoring as described in the USPI.

Thank you. We are happy to take your questions.

Clarifying Questions to Applicant

DR. ALEXANDER: Thank you, Dr. Kramer.

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

Let me call on Dr. Cudkowicz.

DR. CUDKOWICZ: Thank you. I'm Merit Cudkowicz, Mass General Hospital. This question is for Dr. Irizarry, and it has to do, I think, with slide 50. I want a little bit more clarification around the anticoagulant risk, And in particular, I think the last one is anticoagulants and antiplatelets.

Do you have data on just anticoagulants? And also, is the risk higher in APOE4 carriers on anticoagulations? I don't know if the numbers are too small, but I was trying to really sort that risk out more.

DR. KRAMER: Dr. Irizarry?

DR. IRIZARRY: Thank you, Dr. Cudkowicz. The genotypes overall for intracerebral hemorrhage were evenly distributed across homozygous, heterozygous, and noncarriers, and the numbers within those on anticoagulation alone were also distributed across the genotypes.

Let's see. The other question was whether any who were on anticoagulants alone?

DR. CUDKOWICZ: Yes. I know the numbers are

small, but in the last row, they're kind of combined, and I was just wondering if there was a different risk on people just on anticoagulants.

DR. IRIZARRY: Yes. We have those numbers. Let me see. I think they're individual cases of intracerebral hemorrhage, and then I can look through to see what the people were on. Excuse me while we pull that up.

DR. CUDKOWICZ: Sure. No problem. Thank you.

DR. IRIZARRY: No; the individual case numbers.

Among the lecanemab cases with intracerebral hemorrhage in the double-blind phase, there was one on warfarin and aspirin and one on rivaroxaban. So one was on dual and one was by itself. Thank you.

DR. CUDKOWICZ: Okay. Thank you. Just to follow up, it's your belief, or your conclusion, that the risk is not higher for people on these -- or not statistically higher for people on anticoagulation of any type.

DR. IRIZARRY: Well, I think for intracerebral hemorrhage, the rate on subjects that were on both anticoagulants and lecanemab was about 2.5 percent, but the numbers are low, so it is difficult to have a definitive assessment, especially given anticoagulants alone may increase the rates.

DR. CUDKOWICZ: Okay. Thank you very much, and that's all for me, for now.

DR. ALEXANDER: Thanks.

Dr. Follmann?

DR. FOLLMANN: Yes. Thanks. I had a couple of questions. The first one is for Dr. Irizarry.

I don't know a lot about ARIA, but asymptomatic ARIA is not a measure of how a patient feels, functions, or survives, and symptomatic ARIA is often described as self-resolving. So is it thought that ARIA is a predictor or a surrogate for more serious clinical outcome? And if so, what kind of data do you have to support that?

DR. KRAMER: I think we may need to call two individuals to answer that question, Dr. Irizarry

and Dr. Dhadda.

DR. IRIZARRY: ARIA can be serious and life-threatening, so the serious adverse event rate for ARIA-E is 0.8, I believe, and for ARIA-H, 0.6. It's not a surrogate in and of itself of adverse events, but cases of ARIA can be more severe and can cause symptoms and require treatment. For instance, there were three severe symptomatic cases of ARIA-E, one of which had seizure and another which had aphasia, which required hospitalization and, for instance, treatment with corticosteroids.

So the ARIA itself, if it's extensive, can can be serious, but it's not an indicator of any future serious adverse events, if that makes sense.

DR. FOLLMANN: Yes, it does. Thank you.

DR. IRIZARRY: Thank you.

DR. FOLLMANN: Then a somewhat related question, in the slides, you mentioned that ARIA tends to happen early following treatment, and those observations supported monitoring ARIA early in treatment. I'd like to know a little more about what monitoring means. I guess it means to measure

it, but also what are the consequences in terms of patient care? Do you do drug holidays or discontinue therapy, et cetera?

DR. IRIZARRY: Right. There are two components of monitoring for ARIA. The first is obtaining MRIs early on in treatment, the period at highest risk for ARIA. The current label recommends MRI prior to the 5th, 7th, and 14th infusions, and then if ARIA is observed in those MRIs, they would be typically asymptomatic. Depending on the severity of the ARIA, for instance if it's moderate or severe radiographic ARIA, then dosing is paused until radiographic resolution, and then it can be re-initiated.

The other component is in the med guide and warnings, where if patients experience potential symptoms of ARIA, they're then to contact their provider for potential testing. So the current medication guide provides information on the symptoms that should lead a patient or a care partner to contact their physician, and then the appropriate management would be to get an MRI to

identify whether it is ARIA that is causing those symptoms.

DR. FOLLMANN: Thank you.

I have one more question, but I could wait until later. I don't want to take all the question time.

DR. ALEXANDER: You can go ahead.

DR. FOLLMANN: Thanks.

This is for Dr. Cohen. Some of the FDA questions get at the risk-benefit, particularly in subgroups, and I was wondering if you had done quality-of-life analyses within some of the subgroups that the FDA listed, for example, by subgroup APOE epsilon 4 or by anticoagulant therapy, yes or no? So basically, did you do subgroup analysis using quality of life as the outcome?

DR. COHEN: Yes. Thank you for your question. With all of the quality-of-life measures, the randomization strata were examined, and there was benefit for lecanemab. As you recall, one of the randomization strata was APOE4

carrier versus noncarriers, so there was benefit to lecanemab treatment in both groups.

Sorry. Let me just put up a slide for you.

DR. FOLLMANN: Okay. Thanks.

DR. COHEN: Here, what you see is broken down into not just carriers and noncarriers, but the actual genotypes with heterozygous and homozygous. And again, you see for each of the quality-of-life measures, there is benefit on these forest plots for lecanemab treatment, so that's very encouraging.

DR. FOLLMANN: If you look at the bottom right for homozygous, that is numerically not an advantage; correct, or the Zarit's burden? I'm just trying to interpret these. Oh, no, that goes in the other direction, I guess, right?

DR. COHEN: Right.

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

DR. COHEN: You're welcome. Thank you.

DR. ALEXANDER: Thanks, Dr. Follmann.

I have a question for Dr. Irizarry. You

have a one-size-fits-all dosing approach, but seeing from your data, there are subgroups like APOE4 homozygotes who are at increased risk for ARIA. Do you have any data that would suggest that titration of the dose would decrease the incidence of ARIA, especially in those more vulnerable subgroups?

DR. KRAMER: Let me answer that question, Dr. Alexander. It's important to recognize that the rapidity of the clinical response is dependent on the administration of the drug. Slowing of progression was seen with our current dosing at about 6 months. We do have lower ARIA rates than other anti-amyloid therapies already.

Study 201 was a dose and regimen finding study that evaluated five different doses and regimens. The 10-milligram biweekly was identified as the most effective dose. No titration allowed patients to start on the most effective and therapeutic dose from day 1, so we believe we have studied lower doses, understand the projection and modeling of ARIA across time, and that the dosing

currently is the most advantageous.

DR. ALEXANDER: Right. I guess just to follow up, that's an aggregate. My question was, for these specific subgroups like APOE4 homozygotes, would there be any reason, either theoretically or empirically based, to have a titration regimen for a subject who was an APOE4 homozygote, for example?

DR. KRAMER: We have not studied that. We've only studied this single dose, so we're not able to comment on that.

DR. ALEXANDER: Okay. Thank you.

Dr. Gold?

DR. GOLD: Yes. Thank you. This question is for Dr. Dhadda. Actually, it's a two-part question. One, can you help us understand the sample size rationale? These are almost 900 subjects per group, which strikes me as quite large. Then the other part is -- I don't know whether you have it -- it would be helpful to understand the benefit in standardized effect sizes as opposed to just relative percentages. I wonder

if you could help us understand a little bit those parameters of the trial.

DR. KRAMER: Let me ask Dr. Dhadda to comment on that.

DR. GOLD: Great. Thank you.

DR. DHADDA: Yes. The sample size here was estimated based on clinically meaningful 25 percent slowing of decline and 20 percent dropout rate, based on the results from the phase 2 study, including the assumptions on standard deviation. The study successfully confirmed the 25 percent slowing of decline with less than the assumed dropout rate, about 17 percent overall. This sample size also allowed us to actually vigorously look at subgroups to demonstrate the generalizability of results across the various subgroups. Thank you.

To answer your second question, you wanted the standardized effect size. I don't have the numbers right now. We looked at the treatment effect of the absolute treatment difference and percent slowing, and we can do the quick math and

come back to you. Thanks.

DR. GOLD: I appreciate that.

Dr. Alexander, do I have time for a quick follow-up?

DR. ALEXANDER: Go ahead.

DR. GOLD: Yes. In terms of all the secondaries -- and maybe I didn't see this or I didn't catch it -- I understand there was [indiscernible] testing. Was there a control of the type 1 error in terms of hierarchy?

DR. KRAMER: Well, there was no control for that, for the non-specified subgroups. For example, we've been showing many subgroups. Some of the things like quality of life were exploratory endpoints, and therefore there was no multiplicity control for them, for example.

Let me let Dr. Dhadda comment specifically.

DR. DHADDA: Yes. The study was powered for the primary endpoint and the key secondary endpoints, and we had a hierarchical testing strategy, which was met based on the results; however, the study was not powered for each of the

subgroups that were part of the study. Thank you.

DR. GOLD: Thank you.

That's all for me. Thank you.

DR. ALEXANDER: Thanks, Dr. Gold.

Dr. Romero?

DR. ROMERO: Yes. Thank you. Let me lower my hand. A question for Dr. Dhadda pertaining to slides, I guess, 28 through 33.

The handling of missing data, can you quickly comment on the validity of the missing at-random assumption, and then I understand that you also did some sensitivity analyses for a missing not-at-random assumption. Can you comment on those two analyses?

DR. DHADDA: Sure. For most of the intercurrent events, we used the missing-at-random assumption; however, we also performed analysis looking at either censoring the events after the intercurrent events, as well as we used imputation by placebo after discontinuation due to the adverse events or due to the ARIA and infusion-related reactions, all of the key events of interest.

I showed the MMRM on non-randomized patients in the core presentation -- that was on slide 30 -- and the rank ANCOVA multiple imputation approach and the tipping point approach, which is the approach that test the validity of the assumptions on the dropout rate. In addition, for some of these adverse events of interest like ARIA and infusion-related reactions, we also performed analysis using placebo mean for imputation.

Give me one second. Let me find that slide. Can we find the slide with placebo mean? I think it's slide 86 or something.

While we're pulling the slides up, I wanted to comment that all of these analyses had consistent results showing the validity of our assumptions on the single transform [indiscernible], including the -- sorry; I forgot about the log-transformed analysis. Thank you.

DR. ROMERO: Thank you.

DR. KRAMER: We can provide after the break that slide we're looking for.

DR. ROMERO: Thank you. That answers the

question. Thanks so much.

DR. ALEXANDER: Thanks, Dr. Romero.

Dr. Simuni?

DR. SIMUNI: Hi. Tanya Simuni, Northwestern University. A question about the exploratory biomarkers of neurodegeneration, specifically the MRI brain volume and NfL. I recognize those exploratory biomarkers. I assume that Dr. Irizarry probably will be the person to address the question, but thank you.

DR. KRAMER: Yes. Let me ask Dr. Irizarry.

DR. IRIZARRY: In addition to the biomarkers I described for neurodegeneration -- the CSF neurogranin, the CSF total tau that did show benefit -- the results for the volumetric MRI were inconsistent. There was a slight slowing of hippocampal atrophy but greater cortical volume loss with lecanemab versus placebo. The volume loss is not associated with worsening in any of the neurodegenerative biomarkers or outcomes, so the reason for the volume loss is not clear. It could be related to mobilization of amyloid, as shown by

the improvement of amyloid biomarkers, as well as reduction of amyloid-associated dystrophic neurites, as shown by the phosphotau biomarkers and neurogranin, and a reduction in inflammation and gliosis, as shown by the GFAP biomarker.

So it doesn't seem reasonable to conclude that the volume loss itself represents diffuse neuronal loss, and this is likely pseudoatrophy, and certainly the clinical measures indicate a benefit from lecanemab and not a detriment.

With regards to neurofilament light, the CSF neurofilament light was similar between lecanemab and placebo. The plasma neurofilament light showed a trend toward benefit in the lecanemab treatment group at a p-value of 0.06, so we will continue to follow those over time in the open-label extension. Thank you.

DR. SIMUNI: Thank you. A quick follow-up. Is there also a plan to have follow-up imaging in the open-label extension?

DR. IRIZARRY: Yes, there is volumetric MRI in the open-label extension as well.

DR. SIMUNI: Okay. Thank you. You've addressed the questions.

DR. ALEXANDER: Thank you, Dr. Simuni.

Dr. Cudkowicz?

DR. CUDKOWICZ: Yes. Merit Cudkowicz, Mass General. Your population is relatively young, and I know that's because you're targeting early symptomatic, but as it goes on to the broader population, people come in who weren't getting diagnosed before, and we might see an older population. I was just wondering if you have data -- because you went up to 90 -- on the safety and the effect in the older age or anything that would be helpful for clinicians to know.

DR. KRAMER: We, as you mentioned, studied a broad age range, from 50 to 90, and in looking at the adverse event picture across those different age groups, they're very similar.

DR. CUDKOWICZ: Okay. Thank you. That was my question.

DR. ALEXANDER: Alright. Let me ask my fellow committee members if they have any

additional questions. I don't see any hands up.

(No response.)

DR. ALEXANDER: Okay. I think in that case, we will now break for lunch. We will reconvene at 12:30 p.m. Eastern Time.

Panel members, please remember that there should be no chatting or discussion of the meeting topics with other panel members during the lunch break. Additionally, you should plan to reconvene around 12:20 p.m. to ensure that you are connected before we restart at 12:30. Thank you.

(Whereupon, at 11:48 a.m., a lunch recess was taken, and meeting resumed at 12:30 p.m.)

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

(12:30 p.m.)

DR. ALEXANDER: Welcome back.

We will now proceed with the FDA presentations, starting with Dr. Kevin Krudys.

Dr. Krudys?

FDA Presentation - Kevin Krudys

DR. KRUDYS: Hi. I'm Kevin Krudys, and I'll provide a clinical overview of the evidence submitted to support the effectiveness of lecanemab for the treatment of Alzheimer's disease.

Lecanemab is a monoclonal antibody targeting aggregated forms of amyloid. Accelerated approval was granted on January 6th of this year based on reduction in plaques observed in patients treated with lecanemab. The proposed dosing regimen in the submission, 10 milligram per kilogram administered as an infusion every 2 weeks, is the same as the currently approved dosing regimen.

Before discussing the clinical data, it is critically important to address the therapeutic context, as it has been a source of much public

discussion and confusion. Put simply, therapies in this class are not a distinct class of drugs, and much has been made about the 25 failed clinical trials that have tested the amyloid cascade hypothesis, but these previous failures are simply not important for consideration for the results we'll talk about today.

Many of these trials did not enroll patients with brain amyloid pathology, studied doses that were too low, or had questionable target engagement. There was often a lack of proof of concept prior to initiation of phase 3 trials, and most importantly, these previous failures did not study drugs or dosing regimens that reduced brain amyloid plaque in this population to levels consistent with a negative scan.

The newer generation of anti-amyloid therapies targeting aggregated brain amyloid has learned from these previous failures. The evidence from this newer generation of therapies has established that a robust reduction of brain amyloid plaque is associated with a reduction of

clinical decline by approximately 20 to 40 percent over 1 to 2 years.

Now, this relationship has been apparent to us for some time now, and recent results of clinical trials, including the one we'll talk about today, had increased our confidence in that relationship, but our focus today is on the clinical outcome data. The clinical studies that are important to the evaluation of efficacy are Studies 201 and 301.

Study 201 was a placebo-controlled phase 2 study in which the observed reduction in beta amyloid plaques served as the basis for accelerated approval. Although the trial did not technically meet the criteria for success, prespecified analyses suggested a reduction in clinical decline by approximately 20 to 40 percent with the target dose.

This presentation will focus on the results of Study 301 or the CLARITY study. At the time of the accelerated approval, the agency agreed that Study 301 could serve as the confirmatory trial to

verify the clinical benefit of lecanemab, and completion and submission of the study report was issued as a PMR. The applicant has already presented Study 301, so I will only highlight a few key characteristics.

Study 301 enrolled a population that was early in disease progression with evidence of pathology. The presentation will focus on the core phase of the study, as the open-label extension is still ongoing. Among the stratification factors that were used was APOE4 carrier status specified as carrier or noncarrier. The specific genotype was not a stratification factor.

The primary endpoint was a CDR-SB at week 79, and secondary endpoints are listed on this slide in the order of their prespecified hierarchy. CDR-SB assessments were conducted by a clinician who was not involved in patient care and was blind to treatment assignment and safety assessments. There was no single rater that performed all clinical outcome assessments at a single visit. The study incorporated substudies, including PET in

approximately 40 percent of the patients and tau PET in approximately 15 percent of the study population.

The applicant prespecified two efficacy analysis sets. The FAS-plus analysis set included all randomized subjects who received at least one dose at a baseline assessment and at least one post-dose primary efficacy measurement. This is a typical set that we encounter and accept for primary analysis.

Due to the pandemic, the applicant approached us about changing the primary analysis to exclude patients from sites that were closed or on hold for six or more weeks at the peak of the pandemic. As a result, a total of 68 patients, 26 on lecanemab and 42 on placebo, from 19 sites were excluded from the FAS-plus population to define the FAS population for the FDA. The number of patients excluded from the lecanemab treatment arm is approximately 3 percent, and the interpretation of the study results, importantly, was not affected by the choice of the analysis population, as you will

see. For the rest of the presentation, I will mostly show the results for the FAS-plus population, as this is the more complete data set and is consistent with our typical approach.

Study 301 met the primary endpoint, demonstrating a statistically significant reduction in CDR-SB of 0.45 points or a 27 percent reduction of clinical decline at week 79. A similar effect was observed for the FAS population. The magnitude of the treatment effect increased with time, and the effect size translates to a delay in disease progression by 5 months, approximately. The results are robust to sensitivity analysis, including ones that assess the skewness of the data and potential for unblinding.

Public commentary has suggested that an effect size of 1 to 2 points at the group level on the CDR-SB scale is required to show an important effect. I just want to point out that the placebo progression in the trial is between 1 and 2 points as well, so 1.66 points to be exact. So to observe a treatment effect between 1 and 2 points in the

trial will mean that the drug would essentially have to stop disease progression or to reverse the existing decline, which is simply not a realistic expectation at this stage.

Study 301 also met all of its secondary endpoints, including clinical outcome assessments of cognition and function and reduction in brain amyloid load. I want to call your attention to ADAS-Cog14 and to ADCS ADL MCI. These assess cognition and daily function and have been used as co-primary endpoints for AD studies in the past. A reduction in clinical decline for these scales was 26 percent and 37 percent at week 79. Although there is some overlap between the primary and secondary endpoints, each capture distinct information regarding cognitive decline as well. These results provide strong and independent support for the result observed on the primary endpoint.

For subgroups, the results were in favor of the treatment arm for the primary endpoint across all prespecified subgroups of interest defined by

demographic and baseline disease characteristics, except for one, the homozygous carriers. This subgroup made up approximately 15 percent of the overall study population. As seen on the forest plot on the left, the estimate of the treatment effect was 0.28 in favor of placebo or a 22 percent worsening in the treatment arm. If you view this in isolation, this could be a concerning observation of increased risk in this population. It is important, therefore, to review the results of this subgroup in its entirety to provide the appropriate context for the results.

If you look on the right, the longitudinal plot of CDR-SB in this subpopulation shows that the change to CDR-SB is largely similar from week 27 to week 79, with the exception of an unanticipated flattening of the placebo curve between week 65 and 79, which accounts for the 22 percent observation in the forest plot on the left. The longitudinal results are therefore inconsistent with the worsening in lecanemab treatment to this subgroup.

It's critical to also consider results in

homozygous carriers for the key secondary endpoints. Discordant results between CDR-SB and key secondary endpoints have been observed in other clinical trials. Here are the results for both the two key secondary endpoints, the ADAS-Cog14 and ADCS endpoint, that favor lecanemab with point estimates reflecting 13 percent and 25 percent, reduction in decline, respectively.

Similar trends favoring the treatment arm were also observed for health outcome assessments, and importantly, consistent effects on the biomarkers are observed in the homozygous population, suggesting that the pharmacology and the drug action is preserved in this population.

So in summary, there's no expectation before the trial started for a smaller treatment effect in the carriers or for a different treatment effect in the heterozygous and homozygous carriers. In fact, in previous trials, we have seen results that have been variable. Stratification in this study is based on the carrier status and not the genotype, and the size of the population was one of the

smallest tested in Study 301 for homozygotes. So when viewed in their entirety, especially considering the secondary endpoints and the biomarker data, the results support a treatment effect in the homozygous carrier population.

In conclusion, Study 301 was a large trial that demonstrated reduction in the change in the primary endpoint, CDR-SB. The findings in the primary endpoint are supported by statistically significant results for all four secondary endpoints, including clinical endpoints capturing distinct information regarding cognitive decline. Significant effects on the secondary endpoints, including two endpoints, which are independent assessments of cognition and function, provide further support for the meaningfulness of the changes observed on the CDR-SB.

Significant treatment effects were observed in sensitivity analyses, and similar results were obtained in the FAS-plus and for the FAS analysis sets. The treatment effect in Study 301 is supported by the favorable results for primary, and

secondary endpoints across the prespecified subgroups of interest and biomarkers, reflecting target engagement effects on downstream tau pathophysiology, including tau PET and total tau, support the observations on clinical outcome assessments.

With that, I'll conclude, and I'll turn over the presentation to Tristan Massie.

(No response.)

DR. ALEXANDER: You're still on mute, Dr. Massie.

DR. MASSIE: Can you hear me?

DR. ALEXANDER: Now, we can. Go ahead, please.

DR. MASSIE: [Inaudible].

DR. ALEXANDER: Actually, now we don't hear you, or I don't hear you.

DR. SEO: Hi. This is Jessica speaking.

Dr. Massie, we're not able to hear you.

Dr. Alexander, perhaps if we take a minute or two for a break and help Dr. Massie with troubleshooting his audio.

DR. ALEXANDER: Okay. Let's do that. Hopefully, we can resume shortly.

DR. SEO: Okay. Thank you.

(Pause.)

DR. MASSIE: Sorry about the technical difficulty. Hope you can hear me now.

AV TECH: Yes, please go ahead.

FDA Presentation - Tristan Massie

DR. MASSIE: Since we've already heard about the study design, I'll focus on details of the analysis. There are two analysis populations of importance for Study 301 due to considerations related to the impact of the pandemic. First, the full analysis set plus, denoted FAS-plus, which is all randomized patients who received at least one dose of study drug, had a baseline assessment and at least one post-baseline CDR-SB assessment.

Second, the FAS agreed with FDA, denoted FDA FAS, which is a subset of the FAS-plus formed by the exclusion of 68 patients total across both arms at sites closed for six or more weeks during peak COVID period in 2020. Also, due to concerns about

missed doses related to the pandemic, it was decided in December 2020, while the study was ongoing, that sample size for Study 301 was to be increased by 200 patients to a total of approximately 1766 randomized patients.

For the primary analysis, the CDR-SB was to be analyzed by a mixed model for repeated measures, denoted MMRM, in the FDA FAS population to estimate the treatment group difference at week 79. Covariates used in the MMRM model were baseline CDR-SB score; study visit as a categorical effect; baseline score by visit interaction; randomization stratification factors; treatment group; and treatment group by visit interactions.

It is important to note that CDR-SB assessments collected after changes in concomitant symptomatic Alzheimer's medications are included in the primary analysis as specified in the analysis plan. The primary analysis involves no imputation of missing data. It assumes missing data is, quote, "missing at random" or ignorable, but sensitivity analyses were planned and will be

described shortly.

Here we see subject disposition. 1795 subjects were randomized in a 1-to-1 ratio. The full analysis set plus includes 875 placebo and 859 lecanemab subjects. A small percentage did not qualify for the full analysis set due to not having a post-baseline efficacy assessment, a slightly higher percentage for lecanemab. The FAS agreed with FDA involving a small number of pandemic-related exclusions at 833 patients in each arm.

There were 11 percent in each group with post-baseline changes in concomitant symptomatic Alzheimer's medications. Deaths within the 79-week double-blind period were balanced, as shown. Slightly more lecanemab subjects were missing the week 79 CDR-SB assessment, 20.5 percent for lecanemab versus 15.6 percent for placebo.

Here we see the primary result for the difference on CDR-SB at week 79 from the FAS-plus population. The results were consistent between the FDA FAS and FAS-plus populations. Recall that

the FDA FAS differed by having a small number of exclusions related to pandemic-related site closures during the study. The estimated difference was 0.45 on the CDR-SB at week 79 with a p-value less than 0.0001 and a 95 percent confidence interval ranging from 0.23 to 0.67.

Also of interest, in addition to the point estimate of the treatment difference at week 79 is the pattern of differences across all visits in the controlled phase. The figure here shows the effect on CDR-SB being established at week 27 and continuing to grow with increased separation by week 79. Note that the Y-axis is upside down; that is, higher values are lower on the figure rather than higher, to be consistent with worsening going down for some of the other key secondary endpoints. Those results will be described later.

There were numerous sensitivity analyses to check sensitivity to the assumptions of primary analysis and its robustness. Notable among these sensitivity analyses are the tipping point analysis, exploring sensitivity of the primary

result to alternative not missing at random assumptions for missing data; an analysis censoring CDR-SB assessments after initiation or dose adjustment of symptomatic Alzheimer's drugs, or study treatment discontinuation; an analysis censoring assessments after ARIA adverse events; an analysis with imputation like a control patient for the lecanemab arm after study discontinuation due to treatment-related adverse events; and also an analysis in the full ITT population; that is, including those who had no post-baseline efficacy assessments. The sensitivity analyses show that the result of the primary analysis on CDR-SB is reasonably insensitive to the handlings of missing data and intercurrent events; that is, post-baseline events that might be confounding.

Here we see the key secondary endpoints and their results. A hierarchy of key secondary endpoints were specified as shown in the table from top to bottom. Amyloid reduction was the first key secondary, followed by clinical key secondary endpoints. Key secondary endpoint results are

generally supportive with highly significant results that satisfied the hierarchical testing plan, which addressed multiplicity.

To summarize, Study 301 provides statistical evidence of effect for lecanemab with a highly significant treatment difference on CDR-SB of week 79 and similar and supportive results for key secondary endpoints, as shown on the slide here again.

Next, Dr. Erten-Lyons will present the safety data. Thank you for your attention.

FDA Presentation - Deniz Erten-Lyons

DR. ERTEN-LYONS: Hello. I'm Dr. Deniz Erten-Lyons, the clinical safety reviewer for this application, and I will be providing an overview of the safety findings of lecanemab. The current label includes the results of the phase 2 study, Study 201, and my presentation today will focus on the findings from the phase 3 study, Study 301.

The key safety issues we have identified for lecanemab, similar to other monoclonal antibodies directed against amyloid, are infusion-related

reactions and hypersensitivity, ARIA, and cerebral hemorrhage. After a brief overview of safety, my talk will mainly focus on ARIA and cerebral hemorrhage. Specifically, I will review risk of ARIA and cerebral hemorrhage by APOE genotype, risk of cerebral hemorrhage in patients who are on an antithrombotic, and risk in patients with cerebral amyloid angiopathy.

As you can see in this table, there was no imbalance in deaths between placebo and lecanemab. There were more treatment-emergent adverse events on the lecanemab arm compared to placebo. In Study 301, the most common treatment-emergent adverse events, which occurred in at least 10 percent of participants on lecanemab and at least 2 percent or greater than placebo, are shown on this slide. Most of the infusion-related reactions were mild, and most occurred at the time of the first infusion. I will review ARIA-E and ARIA-H separately, shortly in my presentation. Headaches occurred both as a symptom of ARIA but also occurred at a higher incidence on lecanemab

compared to placebo in participants who did not have an adverse event of ARIA captured in the adverse event data set.

I will now briefly talk about ARIA. Monoclonal antibodies directed against aggregated forms of beta amyloid can cause imaging findings known as ARIA. It is hypothesized that anti-amyloid antibodies accelerate breakdown and clearance of amyloid beta. This in turn disrupts vascular integrity and results in leakage into surrounding tissues with parenchymal or sulcal changes observed on MRI. These can manifest as vasogenic edema or sulcal effusion on MRI, known as ARIA-E, or may manifest as ARIA-H or hemosiderin deposition in the form of microhemorrhages or superficial siderosis.

ARIA can occur spontaneously in patients with cerebral amyloid angiopathy, which is a condition where amyloid buildup within cerebral blood vessels leads to fragile vessels that may result in bleeding in the brain. ARIA may also spontaneously occur in patients with Alzheimer's

disease possibly due to underlying cerebral amyloid angiopathy. ARIA-H and ARIA-E can occur together. Most ARIA is asymptomatic; however, serious and life-threatening events such as status epilepticus can occur. When symptoms are present, reported symptoms associated with ARIA include headache; confusion; visual changes; dizziness; nausea; gait difficulty; or other focal neurologic deficits.

I will briefly review the incidence of ARIA in Study 301. Participants on lecanemab had a higher incidence of overall ARIA. Symptomatic ARIA occurred in 3 percent of participants on lecanemab and resolved in most participants without sequela. Risk of ARIA-E was 13 percent on lecanemab compared to 2 percent on placebo. Most ARIA-E occurred during the first 3 months of treatment and majority resolved by 4 months.

Risk of ARIA-H was 17 percent on lecanemab compared to 9 percent on placebo. Most ARIA-H occurred together with ARIA-E. The incidence of isolated ARIA-H, ARIA-H which does not occur together with ARIA-E, was similar between placebo

and lecanemab. There also was a higher incidence of cerebral hemorrhage on lecanemab.

This slide shows the incidence of ARIA and cerebral hemorrhage by APOE genotype. One limitation of this subgroup analysis is the smaller numbers in some of these groups. For example, you will see that only 141 APOE4 homozygote patients were exposed to lecanemab. The main finding in this table is that the risk of ARIA increases in a gene-dose dependent manner, with the number of E4 alleles in both placebo- and lecanemab-treated patients.

If you look through this table from left to right, just focusing on the placebo column under each genotype, and then similarly focusing on the lecanemab column again, going from left to right, you will see the increase in incidence of all types of ARIA as the number of E4 alleles increase in both placebo- and lecanemab-treated patients.

Another finding I would like to point out in this table is that the incidence of ARIA in APOE4 homozygote patients on placebo is higher than the

incidence of ARIA in noncarriers on lecanemab. This further supports the point that ARIA can occur spontaneously in patients with Alzheimer's disease, particularly APOE4 homozygote patients. Within each genotype group, the incidence of ARIA is increased with lecanemab compared to placebo.

In summary, APOE4 homozygotes are at highest risk for ARIA-E and ARIA-H, in general, and during treatment with lecanemab. While the numbers are too small to make any firm conclusions regarding cerebral hemorrhage and APOE4 genotype, more cerebral hemorrhage events occurred in carriers of the E4 allele. This finding was further confounded by the fact that three E4 carriers were on an antithrombotic.

Now, I will review the incidence of cerebral hemorrhage by antithrombotic use. In Study 301, stable anticoagulation used at entry was allowed. Subjects who were on anticoagulants at screening were required to have their anticoagulation status optimized and stable for at least 4 weeks before screening. As you can see, of the six cerebral

hemorrhages, which occurred on the lecanemab arm, three were on an antithrombotic medication. One participant was on ticagrelor, an antiplatelet; one was on warfarin, an anticoagulant, together with aspirin; and one was on rivaroxaban. While the data is limited to make any firm conclusion, it appears that use of antithrombotics, particularly anticoagulation, while on lecanemab may increase the risk of cerebral hemorrhage.

I will now review 3 patients who died during the open-label extension phase of Study 301, with an associated adverse event of ARIA, or cerebral hemorrhage, and on autopsy were found to have cerebral amyloid angiopathy. All three patients were new exposures to lecanemab and had received placebo during the placebo-controlled period of Study 301.

Two of the deaths occurred in patients who were APOE4 homozygotes. Both of these patients had complained of a headache shortly after starting the study drug, and after the third dose of lecanemab, adverse events occurred that ultimately led to the

death of the patients. Autopsy in both of these patients showed presence of advanced cerebral amyloid angiopathy and findings consistent with an inflammatory vasculitis. An additional death occurred in a patient who was on an anticoagulant and experienced a left cerebral hemorrhage after the 9th dose of the study drug. This patient's autopsy showed focal mild amyloid angiopathy with no inflammatory findings.

In both autopsy reports, in the patients who were APOE4 homozygotes, it was mentioned that the inflammatory vasculitis resembled cerebral amyloid angiopathy-related inflammation, which is a rare sporadic autoimmune condition associated with autoantibodies against amyloid beta in the vessel walls. CAA-related inflammation may present with similar clinical and imaging findings to ARIA-E and ARIA-H. APOE4 homozygotes have a higher risk for having underlying cerebral amyloid angiopathy, a higher burden of amyloid angiopathy, and CAA-related inflammation.

Risks of ARIA during treatment with

anti-amyloid monoclonal antibodies may be higher in those with underlying cerebral amyloid angiopathy, particularly in those with a higher burden of vascular amyloid. This said, underlying cerebral amyloid angiopathy is very common in patients with Alzheimer's disease, and not all patients with cerebral amyloid angiopathy will show characteristic MRI findings. For example, one of the APOE4 homozygote patients described earlier did not have any microhemorrhages, superficial siderosis, or cerebral hemorrhage on imaging prior to starting lecanemab to suggest underlying CAA.

Due to the inability to determine the prevalence and severity of underlying CAA in the study population, risks of lecanemab use in patients with cerebral amyloid angiopathy has not been well characterized.

In conclusion, the main risks identified with lecanemab use are ARIA, cerebral hemorrhage, and infusion-related reactions. Risk of ARIA increases in a gene-dose dependent manner with the APOE4 allele and is highest in APOE4 homozygote

patients. Risk in the presence of cerebral amyloid angiopathy or with antithrombotic use is not well characterized. Established risks and uncertainties can be described in the prescribing information. Prescriber and patient education regarding ARIA and surveillance for any new or worsening neurological symptoms, such as headaches emerging during treatment with lecanemab, with follow-up MRI, especially in APOE4 homozygote patients, may mitigate some of the risks of ARIA associated with lecanemab.

This concludes my presentation, and I will now turn it over to Dr. Buracchio for her concluding remarks. Thank you.

FDA Presentation - Teresa Buracchio

DR. BURACCHIO: Thank you to Dr. Krudys, Dr. Massie, and Dr. Erten-Lyons for their presentation, providing an overview of the data from Study 301. As you have heard, the FDA assessments are generally consistent with the results presented by the applicant. Study 301 is a positive study with robust and statistically

persuasive results. The clinical outcome assessments used in the study capture the symptoms and impacts of Alzheimer's disease that are meaningful to patients.

FDA is aware that there is much public discourse about the clinical meaningfulness of the change demonstrated with lecanemab compared to placebo on the clinical endpoints in the study. I would like to clearly state that the agency considers the results of Study 301 to be clinically meaningful.

The agency generally defines clinically meaningful endpoints as those that directly measure how a patient feels, functions, or survives. The easiest way to ensure that a result on an outcome will be clinically meaningful is to use a primary endpoint that is inherently clinically meaningful. With such endpoints, every item or domain in the instrument is considered a measure of clinically meaningful concept for patients, and individual items or domains are scored in a way that any change in scoring reflects a clinically meaningful

change.

The primary endpoint of Study 301, this Clinical Dementia Rating Scale sum of boxes, or CDR-SB, which is shown here, is an example of a scale that is inherently clinically meaningful, and that a change on any individual domain on that scale represents a meaningful change in function for the patient. I will restate some of the points that Dr. Cohen made earlier.

The scale consists of six domains that assess cognition and function and that are scored from 0 to 3, for a total scoring range of 0 to 18. The scoring is based on declines in the patient's previous usual level of function due to cognitive loss and not from impairment due to other factors such as medical comorbidities. For the CDR-SB, the minimal amount of change that they can be scored in a domain is point 0.5, which would be from 0 to 0.5, which indicates progression from no impairment to slight impairment, or from 0.5 to 1, which indicates progression from slight impairment to mild impairment. As shown on this scale, this

0.5 increment measures change in cognition and function that are noticeable and meaningful to patients and their caregivers.

When considering these results, it is very important to distinguish between clinically important individual level change and group level change on the scale. On an individual level, we consider the smallest incremental score change on the CDR-SB of 0.5 to be clinically meaningful. We see that at the group level, the mean difference in Study 301 is approximately 0.5. That means that patients treated with lecanemab had, on average, a half-point less decline on the CDR-SB compared to patients who received placebo.

On an individual level, some patients treated with lecanemab had greater response and some had less, but overall, there were more individuals in the lecanemab group that had less decline on the CDR-SB of at least 0.5 points compared to placebo, and this difference was statistically significant. It is also anticipated that with a drug that impacts underlying disease

biology, that the treatment benefit will increase over time, and that is in fact what we see when we look at the data from Study 301.

When considering clinical meaningfulness, we also looked at support from secondary endpoints. In this situation, we see clear and consistent findings of efficacy on clinically relevant assessments: the ADAS-Cog14 and the ADCS ADL MCI, a measure of activities of daily living, as well as support from health-related quality-of-life measures.

The applicant has also presented a slope analysis that suggests that patients treated with lecanemab were delayed by approximately 5 months from reaching a similar level of decline as the placebo group at the 18-month time point. A delay in disease progression means that patients will prolong the time spent in an earlier stage of the disease where they have greater function and independence. The concepts of delayed disease progression and time saved are undoubtedly clinically meaningful to patients. Overall, the

data provide a compelling case for a clinically meaningful effective lecanemab in patients with Alzheimer's disease.

The safety profile of lecanemab was initially characterized in the phase 2 study that served as the basis for accelerated approval, and the data from that study are described in the current approved prescribing information for lecanemab. As you have heard in today's presentations, the safety findings with lecanemab observed in Study 301 are generally consistent with the findings observed in the original review of lecanemab and described in the prescribing information.

The most frequent adverse events were infusion-related reactions and ARIA, and these are described in the warning section of the current prescribing information. Although symptoms of ARIA when they occur are generally mild or moderate and resolve over time, it is important to note that serious adverse events associated with ARIA can occur.

Although data continue to accrue on the use of monoclonal antibodies that target aggregated amyloid, there remain uncertainties in identifying patients most likely to benefit from therapy and those who may be at risk for serious adverse events. We seek the advisory committee's input on three groups of patients that we have found to present some challenges in characterizing benefit-risk; however, the benefit-risk discussion should not be limited to these groups.

It has been observed in many trials of monoclonal antibodies directed against beta amyloid, including lecanemab, that there is an increased risk of ARIA in the presence of the APOE4 allele, with greater risk observed in homozygotes than heterozygotes. The current prescribing information for lecanemab describes this risk and includes the statement, "Consider testing for APOE4 status to inform the risk of developing ARIA when deciding to initiate treatment with Leqembi."

In Study 301, subgroup analyses by APOE4 status, by carrier or noncarrier, demonstrated a

statistically significant treatment effect in both groups; however, a further subgroup analysis of the carriers by heterozygote and homozygote status suggest that there could potentially be lower efficacy in the homozygote subgroup treated with lecanemab; however, there are limitations to the interpretability of this data such as the small size of the subgroup.

Dr. Krudys describes in his presentation that there is not a mechanistic reason to think that treatment effects of monoclonal antibodies that target aggregated amyloid would be different between homozygotes and heterozygotes, and there are not consistent findings from clinical trials of drugs in this class that would clearly suggest such a difference. We seek input from the advisory committee on whether the efficacy and safety findings from Study 301 impacts the benefit-risk assessment for lecanemab in APOE4 homozygotes.

In Study 301, patients were allowed to be on stable doses of anticoagulants at baseline. There was a small imbalance in cerebral hemorrhage

greater than 1 centimeter occurring in patients treated with lecanemab compared to placebo. There was slightly higher incidence of cerebral hemorrhage in patients taking antithrombotics, but the overall number was too small to allow for definitive conclusions on risk.

The current prescribing information includes the following recommendation regarding the use of antithrombotics with lecanemab based on data from Study 201, in which anticoagulants were not allowed. Because intracerebral hemorrhages greater than 1 centimeter in diameter have been observed in patients taking Leqembi, additional caution should be exercised when considering the administration of antithrombotics or thrombolytic agents; for example, tissue plasminogen activator to a patient already being treated with Leqembi.

We seek input from the advisory committee on whether the findings from Study 301 impact the benefit-risk assessment for lecanemab in patients who require treatment with antithrombotic agents, and if the committee has any additional

recommendations for how to address this potential risk in labeling.

An unanswered question is whether the risk of serious outcomes from ARIA are increased in subjects with underlying cerebral amyloid angiopathy or CAA. Given the background provided by Dr. Erten-Lyons, it is reasonable to hypothesize that the risk of ARIA may be greater in patients with underlying CAA or more severe CAA, and particularly in patients who are APOE4 homozygotes, as they are more likely to have severe CAA.

However, there is a high background rate of CAA in AD, and many individuals with CAA do not have the characteristic findings on MRI. This makes identification of patients with CAA difficult and limits the ability to make specific recommendations to mitigate any increased risk of ARIA if CAA does pose an increased risk.

As described in Dr. Erten-Lyons presentation, there are individuals with identified CAA pathology who have had serious outcomes during treatment with lecanemab, and some of those

patients did not have MRI findings suggestive of CAA. However, given the high background rate of CAA, there are also many individuals who have likely received treatment with lecanemab who have CAA pathology and have not experienced significant adverse events.

The current prescribing information does not specifically address the potential risk of lecanemab use with CAA but does list risk factors for intracerebral hemorrhage that are associated with CAA, such as prior cerebral hemorrhage greater than 1 centimeter and greatest diameter, more than 4 microhemorrhages, superficial siderosis, and evidence of vasogenic edema.

The prescribing information states that caution should be exercised when considering the use of Leqembi in patients with these risk factors. We ask the advisory committee if it has any additional recommendations for how to address any potential risk of lecanemab use in patients with CAA and labeling.

The division believes that it is important

for prescribers, patients, and caregivers to be aware of the potential risks associated with the use of lecanemab with clear labeling. The decision to initiate therapy with lecanemab should be made with an informed discussion between prescribers, patients, and caregivers with consideration of the potential benefits and risks.

I will end with our questions for the advisory committee today. As I noted earlier, we are seeking input on the verification of clinical benefit for a drug that has already been approved based on a reasonably likely surrogate endpoint. There are identified risks with lecanemab that are already described in the currently approved prescribing information. We ask for your consideration of the efficacy and safety data from Study 301, and if it influences or changes the benefit-risk assessment for lecanemab for the treatment of Alzheimer's disease.

I now return the proceedings to Dr. Alexander for any clarifying questions from the panel.

Clarifying Questions to FDA

DR. ALEXANDER: Thank you, Dr. Buracchio.

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

We'll start with Dr. Cudkowicz.

DR. CUDKOWICZ: Hi. Merit Cudkowicz. I'm not sure who is the best person to address this to, but I wanted to understand a little bit more the FDA's thoughts on the risk in people with CAA, in

particular, people in the open-label extension who have the inflammation as well.

Was that something that was picked up before on the MRIs? I'm just thinking if there's a way to screen for that before something that you might exclude people from, if you knew ahead of time that they had CAA with some inflammatory changes.

DR. BURACCHIO: I'll ask Dr. Erten-Lyons if she could take that question.

DR. ERTEN-LYONS: Yes. I'm happy to take that question. Of the 3 patients who died during the open-label extension period, their MRI scan, conducted prior to the first dose of lecanemab in the open-label extension phase, showed microhemorrhages in the APOE3 carrier patient, who was 88 years old when he died, so he had 3 microhemorrhages. One of the patients who died after TPA administration with multiple cerebral hemorrhages did not have any microhemorrhages on MRI, and there's some conflicting information on the number of microhemorrhages on MRI on the patient who died due to severe ARIA-E and ARIA-H

and related complications. In her case, a publication reported 4 microhemorrhages on that MRI, and we at the FDA reviewed the images and thought there were at least 3 microhemorrhages, but the study MRI readers reported zero microhemorrhages on that patient. So there is some disagreement on that participant, but at least one of them for sure did not have any microhemorrhages. Thank you.

DR. CUDKOWICZ: Thank you, for your answer.

DR. ALEXANDER: Let me just follow up on Dr. Cudkowicz's question. As Dr. Buracchio noted, the label for the study, the CLARITY study, excluded subjects who had significant levels of pathology on MRI above certain thresholds, but the current label allows prescribing to those people. It just says use caution.

Can you elaborate on the rationale for not prohibiting the use of lecanemab in people that have significant pathology, as measured by MRI at baseline?

DR. BURACCHIO: Yes. I'm going to turn this

question over to Dr. Yasuda to answer.

DR. YASUDA: Thank you. This is Sally Yasuda. Contraindications are appropriate when the risk from the use of a drug clearly outweighs any therapeutic benefit, and should only be used for known risks, not theoretical risks. And at this point, because CAA seems to be very ubiquitous in the Alzheimer's disease population, and you heard about the uncertainties regarding the risk of CAA and its interaction with lecanemab and interaction with Alzheimer's disease patients, and the risk of ARIA, we think that the added risk from all those things combined is still a theoretical risk. So in this case, we think a warning is appropriate until we understand this a little bit better.

DR. ALEXANDER: Okay. Thank you, Dr. Yasuda.

Dr. Follmann?

DR. FOLLMANN: Yes. Thanks. Well, let me start out with some prepared questions. The first one has to do with the APOE4 subgroup, where you noted that in the efficacy analysis, it was

trending in a negative direction compared to the other subgroups, and I was wondering if you had done a statistical test of interaction, where you test whether the efficacy estimate for APOE4 homozygous is statistically different from those who aren't APOE4 homozygous.

When I'm interpreting subgroups, I'm wary of looking at the estimates of the confidence intervals, and I like to do a formal test of whether they're different, which incorporates the small sample size as part of the test for the APOE4 subgroup. So anyway, that was a question to either you or the sponsor, if you've done a test of interaction for that.

DR. BURACCHIO: I will ask Dr. Tristan Massie if we have done that, and if we have not, then I would ask the sponsor if they have looked at that.

DR. MASSIE: This is Tristan Massie. I did an exploratory test looking at the three carrier groups -- carrier, noncarrier, homozygote and heterozygote -- and got a p-value of 0.0166 for

that 2-degree of freedom test, but we don't think it's a qualitative interaction necessarily. The strength of the interaction doesn't seem to be qualitative.

DR. FOLLMANN: Okay. Thank you for that.

One of the questions has to do with the anticoagulant subgroup, and we looked at adverse events by that, and the sponsor, in particular, I remember did that. But I was wondering if you had done an efficacy analysis where you look at the anticoagulant subgroup and the group that was not anticoagulant, because when you find no balance in risk and benefit, you've shown us the risk potentially, but not the benefit. I assume it's similar whether you're on anticoagulants or not, but I'd just like that confirmed or some analysis to that effect.

DR. BURACCHIO: I don't believe we have done any analysis like that. I wouldn't expect that use of anticoagulants would have an interaction on that, but I would ask Eisai if they have done that analysis.

DR. KRAMER: [Inaudible].

DR. ALEXANDER: I think you're on mute,

DR. KRAMER: Yes, we have done that analysis. Let me show you this slide.

So as you see, we did this analysis for a number of medications. If you look at the second group down, anticoagulants, slowing of decline, 52 percent in that group, but that's a small group.

DR. FOLLMANN: Okay. Thanks.

I have one more question I think that harkens back to what Dr. Alexander was talking about earlier. Usually in a trial, there's inclusion/exclusion criteria, and then you generalize the results of the study to the population that you defined by inclusion/exclusion criteria. But you're not doing that really here, as was pointed out before, where people who had I guess what might be called severe CAA at baseline were excluded but have a warning in the label. I'd just like to hear a little more discussion about the rationale for that. I know you mentioned it briefly, but maybe a little more discussion.

DR. BURACCHIO: Well, I'll start. Our labeling requirements, our guidelines for labeling, are really data driven, so we look to see what data we have in a given population to inform labeling. The absence of data in a population does not necessarily lead to a contraindication in that population.

As Dr. Yasuda said, a contraindication is for known risks, and the risks that might be anticipated with CAA findings on MRI, such microhemorrhages, white matter changes, it seems reasonable, from a clinical practice standpoint, to consider those factors when you're doing your assessment of whether you think that patient would be a good candidate for treatment with lecanemab, but we don't really have any data to say that those should be excluded. And as Dr. Yasuda said, our criteria for writing contraindications in a label are really dependent on having a known risk, which is either you have data or the rationale was so compelling that it could be considered a known risk. I think we're still viewing this as there's

a fair amount of uncertainty and we don't yet consider it to be a known risk.

DR. FOLLMANN: Right. I mean, maybe you suggested, or maybe I was thinking this, that you were going to be monitoring this going forward, and then you would know better whether this group that was excluded in the trial, in fact, did have a higher risk. Do you have any specific plans for that?

DR. BURACCHIO: We don't have any specific plans other than to continue our usual postmarketing pharmacovigilance.

Dr. Yasuda, I know we have some enhanced pharmacovigilance, and I'm not sure if that addresses this specific point.

DR. YASUDA: We currently, since the accelerated approval, have had enhanced pharmacovigilance in place, where the sponsor reports to us twice a year about the risk of ARIA and the risk of cerebral hemorrhage with various risk factors considered. We don't specifically discuss CAA in that request, but that's certainly

something that could be added to it.

DR. BURACCHIO: Yes. If we go to slide 70, I think we have the language of the enhanced pharmacovigilance there. We do ask for recording of any cases of hemorrhage, cases of vasculitis, and we ask for, as part of any reporting of those cases, any additional data that can be provided to help characterize that risk.

DR. FOLLMANN: Yes, it ideally would include MRIs or information before the event happened, and then you could better describe the risk in that group that was excluded at baseline.

DR. BURACCHIO: I'll just also note that as you have your discussion later, if you have any specific recommendations on things that we should consider, we would be happy to hear those.

DR. FOLLMANN: Yes. Thanks. That's all I have.

DR. ALEXANDER: Thanks, Dr. Follmann.

Dr. Romero?

DR. ROMERO: Thanks. I had the same question as Dr. Follmann, so thank you, Dr. Massie,

for answering the question about interactions, but the next question probably is more for Dr. Krudys, pertaining to slide 17 and 18.

The first point, and I'd like you to comment on this, is that the interpretation of the results in the homozygous needs to be put in the context that the stratification was done based on carrier status, not genotype. That's point number one. Then point number two, the fact is that the interpretation is, essentially, that we don't know which direction things go in the homozygous.

Have you evaluated the underlying rate of progression in that subpopulation in the control arm? Again, the question is can you comment on the potential of that being the hardest-to-treat population and, hence, the low frequency of that population, and then the hardness of how to treat that population and how that factors into these results?

DR. KRUDYS: It's Kevin Krudys here. I can start with an answer. You're asking about the progression in the homozygous population in the

placebo group, and they actually had the slowest placebo decline of the four groups shown on this slide. We've looked at some other trials as well, and it's not quite consistent in terms of who has the fastest progression or slowest progression. You do see some variability between trials in the rates of progression in these four groups.

DR. ROMERO: Thank you. That answers my question.

DR. ALEXANDER: Dr. Gold?

DR. GOLD: Thank you. Questions to either the FDA or the sponsor. In the CAA literature, there are a number of reports that talk about anti-amyloid antibodies present, where titers are going up during the course of CAARI. And I'm wondering whether in your discussions, in the sense of identifying risk factors, particularly in that interaction with the CAA-RIs, also known for APOE, has there been any thought given to actually looking for anti-amyloid antibodies at baseline before somebody gets treated if they have, for example, combination of APOE4 or some titer or

anti-amyloid antibodies, and maybe that would not be an appropriate person to treat. That's my question. Thank you.

DR. BURACCHIO: [Inaudible].

DR. SEO: Dr. Buracchio, this is Jessica. You're muted if you're speaking.

DR. BURACCHIO: Sorry. Thank you.

I don't believe that we have looked at that, so I would ask the sponsor if that is something that they've considered.

DR. KRAMER: Can you hear me? The answer is no; we really haven't looked at that.

DR. GOLD: Okay. Thank you.

DR. ALEXANDER: Dr. Simuni?

DR. SIMUNI: I have a question for the FDA team regarding the current language about APOE4 status testing and what will be considered in the revisions of the USPI. It might be better fitted into the discussion part of this meeting, but today's language, as Dr. Buracchio has shown in the slides, indicates to consider testing for APOE4 status to inform the risk of developing ARIA. So

obviously, that is based on the 201 study that gets 6 percent of homozygotes -- [dog barking] -- I apologize; that's my dog.

The 301 study has 15 percent, which still is a small percent, so if we double-test the patients started on therapy, we will have difficulty informing the field that the genotype is relevant risk, which based on the current study, certainly it is the genotype and the dose effect. So I wanted to hear FDA's comment.

DR. BURACCHIO: I would say, yes, when we reviewed the data for 201, I think we had limited data in APOE4 homozygotes from that study. We have more data currently. One consideration that we have to give is that APOE4 genotype testing is not really standard in most clinical evaluations at this time, although that may change over time. And particularly in light of the therapy, and if the therapy becomes -- well, it is already available under the accelerated approval pathway, but should it get traditional approval, it may lead to more widespread use, so standards for testing may

change. Right now, it's hard to say more than consider because it isn't a standard test that's done, but that might be a more strong recommendation that we could consider.

Dr. Yasuda, did you have a comment that you wanted to make on this?

DR. YASUDA: No. I would just say we have acquired more information with 301, and we will be updating the label with more information about that. Of course, we see this across the class, so this is considered class labeling.

DR. SIMUNI: Thank you. That addresses the question.

DR. ALEXANDER: Thanks, Dr. Simuni.

I just want to come back to this discussion about contraindication versus warning, and I understand that FDA wants to use actual data to determine if something is a contraindication unless there's a strong theoretical risk. My question is whether there's any data available from other anti-amyloid antibodies. I imagine that they have similar exclusion, they're clinical trials, but

perhaps from the postmarketing experience of aducanumab, that would inform on this theoretical risk of MRI indications of CAA, and then risks of ARIA.

DR. BURACCHIO: I can't speak specifically to the aducanumab data sets, but I can just say that there's only limited experience, and the little experience that we have is usually from patients who have developed findings while they're on treatment already. During the course of the study, they're mostly excluded at the baseline, but then during the study they may develop more microhemorrhages.

Some studies have had exclusion cutoff at the higher level of 10 microhemorrhages or higher that you would stop dosing in those patients if they had already been started, but we do still end up getting some data on people who may continue to accrue hemorrhages during treatment or develop white matter changes during treatment. Right now, we don't have a whole lot of experience with those patients to really be able to draw any conclusions,

but that would be, I think, where the very limited data that we have would be coming from.

DR. ALEXANDER: Okay. Thanks. Thanks, Dr. Buracchio.

Let's see if there are any other questions from the committee and give everyone one last chance here to ask FDA.

(No response.)

DR. ALEXANDER: If not, I guess we'll take a 15-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, and we'll resume at 2:00 Eastern Time. Thank you.

(Whereupon, at 1:39 p.m., a recess was taken, and meeting resumed at 2:00 p.m.)

Open Public Hearing

DR. ALEXANDER: Welcome back. 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 this open public hearing to be conducted in a fair and open way, where every participant is listened to carefully and treated with dignity, courtesy, and respect. Therefore, please speak only when recognized by the chairperson. Thank you for your cooperation.

Can I ask speaker number 1 to please unmute and turn on your webcam?

DR. SALLOWAY: Can you hear me? Oh great.

DR. ALEXANDER: Yes. Will speaker number 1 begin and introduce yourself? Please state your name and any organization you are representing for the record. You have three minutes.

DR. SALLOWAY: I am Stephen Salloway, professor of neurology and psychiatry at Brown Medical School and associate director of the Brown

Center for Alzheimer's Disease Research. I'm an expert in Alzheimer's disease and the management of ARIA. I have been a site PI and safety monitor for trials of lecanemab, aducanumab, donanemab, and gantenerumab, and I have provided long-term treatment to more than 45 patients on lecanemab in the CLARITY and AHEAD trials. I have been a consultant to Eisai, Biogen, Lilly, and Roche, and I am a member of the ADRD therapeutic working group and an author of the appropriate use recommendations for lecanemab and aducanumab.

The positive clinical outcomes in the phase 3 trial of lecanemab, which is supported by positive clinical outcomes in the phase 3 trial of donanemab, demonstrate that amyloid-lowering antibodies can produce clinically meaningful benefits that warrant full FDA approval. The selection of appropriate patients for treatment is critical for ensuring optimum outcomes. The prescribing information should follow the lecanemab phase 3 criteria, supplemented by additional safety recommendations from disease experts. Benefits

should be weighed against potential risks, with careful safety monitoring by a trained and experienced clinical team.

The following is recommended for clinical use, which you can see on the accompanying slide: early AD with amyloid confirmation; no MRI safety exclusions or unstable medical conditions; testing for APOE; no treatment with anticoagulants; informed consent from the patient and family; MRI safety monitoring during the first year of treatment; and management of ARIA for the phase 3 protocol and appropriate use recommendations.

The main side effect of amyloid-lowering antibodies is ARIA, which is usually transient and asymptomatic. The overall rate of ARIA is lower for lecanemab than for other amyloid-lowering antibodies, but serious and fatal cases related to treatment have occurred. The goal is to limit the number of serious outcomes.

APOE carriers, E4 carriers, and especially E4 homozygotes have a higher rate of ARIA and are more likely to have a more serious event. The

numbers are small, there's a higher rate of microhemorrhage in patients on lecanemab and anticoagulation, and the appropriate use recommendations have recommended not to treat patients on anticoagulation with lecanemab until further safety data is available.

The results of the phase 3 studies of lecanemab and donanemab represent a breakthrough in the treatment of early Alzheimer's disease, and I support full FDA approval for lecanemab, with a strengthened label that provides clear guidance on patient selection and safety monitoring. Thank you.

DR. ALEXANDER: Thank you.

Could I ask speaker number 2 to please unmute and turn on your webcam? Will you begin and introduce yourself? Please state your name and any organization that you're representing. You have three minutes.

MR. VRADENBURG: My name is George Vradenburg. I'm the executive chairman and co-founder of UsAgainstAlzheimer's, a

patient-centric, nonprofit organization. I'm also from a family with three generations of Alzheimer's disease. I've no personal financial disclosures. My organization is a nonprofit that receives programmatic support from Eisai, its competitors, and thousands of other donors.

At the risk of stating what this committee already knows, Alzheimer's is a devastating, progressive, and ultimately fatal disease. It takes independent people, first makes them forgetful, advances to a point where we need some help with a few tasks, then more help with more tasks, and finally to a point we're unable to care for ourselves and often have hallucinations, paranoia, agitation, and/or aggressiveness. In late-stage Alzheimer's, the person's completely dependent on others, and then we die.

That's why disease modification is so important. Slowing this relentless, terrible tragedy at its early stage before we lose our independence is critical, and life-enhancing, and life-extending. Patients have told us, quite

clearly, and we ask the committee to consider patient-reported preferences research alongside the clinical trial data, so well reported by Dr. Sharon Cohen.

We have published our scientifically rigorous research on what matters most to patients and three articles in peer-reviewed journals submitted in our written comments and cited in the Eisai submission. What we found is not ambiguous. People at early stages of the disease tell us that what they want most from the therapy is stopping or slowing progression. They define progression more broadly than just what CDR sum of the boxes captures. Activities of daily living matter a lot. Functional performance matters a lot. Not being a burden to others matters a lot. Self-awareness matters a lot. Quality of life matters a lot.

It was really heartening for us to see that lecanemab moved the needle not just on one measure, but on all of these measures, ADLs by 37 percent versus placebo, but every secondary and quality-of-life measure showed that lecanemab was slowing

progression, improving the lives, and extending the lives of people on drug and their caregivers. We cannot ignore side effects, and that's true of most drugs, and we've heard some side effects today, potentially more risk for homozygotes and for those on some underlying CAA condition.

Some academics claim that patients are desperate, that our needs should be discounted, but patients and their families make reasoned and clinician-informed, benefit-risk calculations every day, including on cancer medicines, MS medicines, HIV medicines. Patients give informed consent for all manner of medical decisions, whether we're homozygotes, or whether we have some known risk of a disease, or maybe even if the risks are not yet known, but we also need to take the fact that people that are living with Alzheimer's need a treatment urgently.

DR. ALEXANDER: Mr. Vradenburg, I just need you to wrap up your comments.

MR. VRADENBURG: Yes.

This committee should act with clarity and

decisiveness on our unmet need, the urgency of addressing it, and approve the full approval of lecanemab with confidence that people living with Alzheimer's will find the delay in progression to be meaningful and important. Thank you for the time.

DR. ALEXANDER: Thank you.

Speaker number 3, please unmute and turn on your webcam. Please state your name and any organization you are representing, for the record. You have three minutes.

DR. ZELDES: Good afternoon. I am Nina Zeldes, a health researcher at Public Citizen's Health Research Group. Public Citizen's Health Research Group has no financial conflict of interest, and I have no financial conflict of interest. Public Citizen strongly opposes FDA's approval of the supplemental biologics license application of lecanemab for the treatment of Alzheimer's disease because the evidence for the drug's benefit does not outweigh its significant risks.

The evidence of lecanemab's efficacy is based on Study 301. Although the primary endpoint was statistically significant, the treatment difference between lecanemab and placebo was 0.45 on a scale that ranges from 0 to 18. In fact, in a New England Journal of Medicine article, lecanemab investigators on the results of this study verified that for this endpoint, quote, "A definition of clinically meaningful effect has not been established," end quote. Secondary endpoint measures similarly yield the treatment effects that were small compared to the range of values for the instruments, suggesting the effects of the drug on function may not be clinically meaningful.

Despite all the spin [ph] and lobbying for drug approval, the FDA has not been provided with evidence of clinical benefit for lecanemab that is clearly compelling. The new information highlights the concerning patient safety data, which include ARIA, cerebral hemorrhage, and infusion-related reactions. For example, ARIA occurred in 21 percent of patients treated with lecanemab

compared to only 9 percent in the placebo arm, and infusion-related reactions were 3.7 times as likely with lecanemab.

Lecanemab was also associated with a decrease in brain volume and cortical thickness, which may, as FDA noted, be indicators of atrophy and neurodegeneration, making it necessary to, quote, "Collect longer term data in a large umber of patients to further understand the clinical implications."

A first step towards providing the necessary additional data was Study 301's open-label extension. The results reinforced the serious safety concerns such as ARIA, and showed the treatment with lecanemab was associated with 3 deaths. Based on the available evidence about efficacy and safety, we urge the committee to vote no on the voting question and recommend to the FDA that the supplemental biologics license application not be approved. Thank you for your time.

DR. ALEXANDER: Thank you.

Speaker number 4, please unmute and turn on

your webcam. Please state your name and any organization you're representing, for the record. You have three minutes.

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. The LEAD Coalition has complete confidence in the scientific rigor of FDA's process and the judgments of its world-class neuroscience experts. We commend FDA's commitment to person-centered and patient-focused understanding of clinical meaningfulness.

I have two disclosures. First, the sponsor is a LEAD Coalition member; 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, which I am not in any way

representing here today.

Like many of you, I've known thousands of people with the lived experience of Alzheimer's, and 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 while my father's losses were heartbreaking for us and for him, he was spared the worst cruelties that so many others experience.

Nomenclature notwithstanding, the early stages of Alzheimer's disease are mild only in comparison to the even more brutal stages that follow, as surely as day follows night. Our loved ones, our families -- not doctors, not payers, not politicians -- we define what is clinically meaningful. For us, slowing the progression of this otherwise relentlessly devastating disease and its impacts on quality of life by 6 months to a year surely is clinically meaningful. It is a godsend. It gives us more time when that time is most meaningful; more time when that time is most

precious; more time when that time contributes most to the quality of life; and more time when for some of us, it might buy us enough time for the next generation of improved therapies to become available and bless us with even more time in this early stage of disease.

We understand that first generation treatments are not a panacea. They are not cures. They are not without risks. But we also understand, as others should understand, too, that to make progress, we must start where we are, with treatments that require our expectations to be measured. Today, we see a treatment that significantly slows decline in cognition and function, particularly in activities of daily living; a treatment that meaningfully preserves measures of independence, dignity, and autonomy that we hold dear.

Today, you will help determine whether our hopes and our 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. ALEXANDER: Thank you.

Speaker number 5, please unmute and turn on your webcam. Please state your name and any organization that you're representing for the record. You have three minutes.

DR. PIKE: Thank you. My name is Joanne Pike. I am the CEO and president of the Alzheimer's Association and the Alzheimer's Impact Movement. The association received 1.06 percent of its total 2022 contributed revenue from the biotechnology, pharmaceutical, diagnostics, and clinical research industries. The association received $465,000 from Eisai in fiscal year 2022. This and additional information can be found at alz.org/transparency. The vast majority of our funding comes from individuals. I have no personal disclosures.

On behalf of the Alzheimer's Association, all those living with Alzheimer's disease, their caregivers and their families, we are grateful to

the FDA for convening this advisory committee to discuss the traditional approval of Leqembi, an anti-amyloid treatment that reduces cognitive and functional decline in individuals with early Alzheimer's disease. In the Alzheimer's Association's written statement, we present a comprehensive review of the case for recommending to the FDA that it grant traditional approval for Leqembi.

In these remarks, I would like to emphasize two points from that submission, the high degree of consensus in the Alzheimer's research community for FDA approval and the clear case for Leqembi's clinical meaningfulness. That consensus was perhaps best captured by the common practice, sign-on letter sent to CMS and included as an attachment to our written comment that had been prepared last December, shortly after CLARITY AD results were revealed. Among the over 200 scientists and clinicians who signed on were researchers who were and are highly skeptical about the strength of evidence for Aduhelm, but there is

little to no doubt among our communities' most experienced clinicians and trialists that Leqembi amply clears the bar set by the FDA for traditional approval.

Unfortunately, there is one particular important aspect of the evidence where their remains unnecessary confusion. It is the practical meaning of Leqembi's clear efficacy results. First, it is clear that Leqembi delivers more time to those still in the earliest stages of Alzheimer's and mild cognitive impairment, almost half a year in the course of only an 18-month trial. These are very significant results compared to what is typically achieved with new routinely approved and welcomed therapies for other progressive and fatal diseases.

Second, as reflected both in written and oral comments to this committee from those who have experienced this terrible disease firsthand, this extended time of independence and rich interaction with loved ones in the world around them is of tremendous value. The most disturbing aspect of

some discussions about clinical meaningfulness are those speculating about and often misinterpreting the meaning of changes on a scale like the CDR sum of boxes to diminish the importance of these treatments to those who have early Alzheimer's.

The additional time provided by these treatments is clear. The value of this time is also clear when you listen directly to those who would benefit. In contrast, in many discussions, the term "modest" is confidently used by journalists and commentators to describe the impact of these treatments. That's a qualitative term that reflects an ethical judgment versus the true clinical impact --

DR. ALEXANDER: Sorry to interrupt --

DR. PIKE: -- and gaining an average of almost half a year of rich, independent living in just a span of 18 months is anything but modest, but it is profoundly important.

DR. ALEXANDER: I need you to wrap up, please.

(Crosstalk.)

DR. PIKE: Leqembi is a profoundly important advance for our community. With any firsts, there remain unresolved issues to consider such as representation and safety in real-world settings, but it deserves celebration. It should receive traditional approval, and all appropriate individuals should have full access to it without barriers. Thank you.

DR. ALEXANDER: Thank you.

Speaker 6, please unmute and turn on your webcam. Please state your name and any organization you are representing, for the record. You have three minutes.

DR. ZUCKERMAN: Do you have my slides?

DR. ALEXANDER: Can we put her slides up?

DR. ZUCKERMAN: Thank you.

I'm Dr. Diana Zuckerman, president of the National Center for Health Research. My comment today will rely on my research experience at Yale and Harvard and in my current position, my expertise on FDA policies, and with my dad with dementia.

The National Center for Health Research is a nonprofit think-tank that focuses on the safety and effectiveness of medical products, and we do not accept any funding from companies that make those products, so we have no conflicts of interest.

Let's talk about efficacy. It was important to see that there was statistically significant reduced scores on several cognitive outcome measures, and FDA says that these are clinically meaningful, but we disagree with that. The reason why we disagree -- let me say, it could be true or it might not be meaningful -- is that the differences are small, and because MCI varies due to social interactions, depression, and other non-pharmacological factors.

In fact, neurologists at the American Academy of Neurology have published numerous articles talking about the fact that up to 50 percent of people with mild cognitive impairment revert to non-impaired status by themselves, without any kind of pharmacological intervention. There was a recent JAMA article on this, it's on

the Harvard Medical School website, and also a Mayo Clinic website, and many other places.

So when you think about the fact that up to half of the people who have mild cognitive impairment will get better without a drug, look at these known adverse events, which you've already heard about, look at the risk factors you've also heard about, and keep in mind that 22 percent of the patients on Leqembi discontinued their study participation compared to 17 percent on placebo.

Diversity was also a problem with blacks, only 2.3 percent, and that was only 20 patients taking Leqembi. The statistics for Asians were better, but most of them, almost all of them, were living in Asia, and in those patients, apparently, there was no benefit. Other racial groups, 2.4 percent, again about 20 people, and Hispanics, the representation was better.

When we think about what's known and unknown, we think about the possibility of deaths and other very serious adverse events that clearly show up, and think about the fact that MRIs were

much more frequent in the study population than is recommended on the label or would be the case in real life, and the fact that data clearly show that mild cognitive impairment does not mean that Alzheimer's is inevitable, even for people who have amyloid plaque on their brains. Many of these people, up to 50 percent of them, will get better without any drug.

So think of that compared to what the risks are; and I do wonder why FDA didn't discuss the fact that Alzheimer's is not inevitable for this population. That's terribly important.

DR. ALEXANDER: Can I ask you to finish your remarks?

DR. ZUCKERMAN: Yes. I am done. Thank you very much for the opportunity to speak today.

DR. ALEXANDER: Thank you.

Let me just ask all our speakers to try to adhere to the three-minute limit, so we can hear from everyone.

Speaker number 7, please unmute and turn on your webcam. Please state your name and any

organization you're representing, for the record. You have three minutes.

MS. PESCHIN: Thank you. Hi, everyone. I'm Sue Peschin, and I serve as president and CEO of the Alliance for Aging Research. The Alliance receives funding from the sponsor and competitors for non-branded public policy work on Alzheimer's disease.

In her opening remarks, Dr. Buracchio reminded everyone that Leqembi was already approved by the FDA six months ago under its accelerated approval pathway. The FDA may grant accelerated approval for medications that treat severe, life-threatening, or rare diseases when patients have no treatment options or run out of existing ones. Dr. Buracchio then explained the differences and similarities between accelerated and traditional approval; most notably that the FDA requires substantial evidence of effectiveness for both types of approval.

It was a useful 101 presentation, but it made me wonder why was it needed. Maybe because

14 months ago, CMS announced that there wasn't enough evidence for Medicare to cover and pay for any of the early Alzheimer's medications. That final decision in April 2022 was the first time CMS had declined to cover a drug for its FDA-approved medically accepted use. It was also the first time CMS denied coverage for an entire class of drugs, based on clinical trial data for a single drug before any data of the other drugs in the class were available.

The public's trust in science and government has seen better days. Misinformation and disinformation are rampant. In CMS' quest to prioritize financial risk over health risk, the agency is recklessly selling doubt about the science on Leqembi and about FDA's scientific and regulatory authority to determine the safety and efficacy of it. It's not CMS Administrator Brooks-LaSure's place to challenge the FDA's use of accelerated approval, just as it's not the remit of Commissioner Califf to publicly opine on drug pricing. This overstepping by leaders at sister

health agencies has to stop.

Recent polling data from Lake Research Partners and public opinion strategies show that voters really don't like the exception CMS is making when it comes to covering the cost of Alzheimer's treatments. Nearly 90 percent of voters polled believe Medicare should be required to cover the cost of FDA-approved drugs that slow the progression of Alzheimer's. No other recent polling on core values, from religion to even tolerance for others, even comes close.

To the advisory committee, please consider how your dialogue today will help or harm the public's trust in science and in the FDA. Please serve as true advisors to the FDA's already impartial, rigorous, and expert review. And to those of you listening at the White House, we need your help to make this right for people living with early Alzheimer's. You can't sit this one out because you're in charge, and it won't happen without you. Thank you.

DR. ALEXANDER: Thank you.

Speaker 8 wasn't able to attend today, so we'll move on to speaker 9. Please unmute and turn on your webcam. Please state your name and any organization you're representing, for the record. You have three minutes.

MS. JONES: Thank you. I'm Karyne Jones. I'm president and CEO of the National Caucus and Center on Black Aging, NCBA. I'm speaking today to ask you to consider the perspective of people from underserved communities who are living with early Alzheimer's and in support of traditional approval of Leqembi as you discuss treatment of mild cognitive impairment and mild dementia due to Alzheimer's disease. In disclosure, NCBA receives funding from sponsors for non-branded health education and advocacy. I have no personal disclosures, and I do serve on the Alzheimer's Association Board.

Racial and ethnic communities have been historically underrepresented in clinical trials. Alzheimer's and dementia affect everyone, and because black and Hispanic Americans are

disproportionately impacted, we must hold researchers accountable to a higher standard of inclusive recruitment practices for clinical trials so that discoveries made will benefit all. It is an important step in the right direction that about 25 percent of the U.S. participants in the CLARITY AD trial were black and Hispanic.

People of color are of higher risk of Alzheimer's and often diagnosed at younger ages of onset and later stages of disease, and with more comorbidities. Stigma, cultural differences, the ability to obtain a diagnosis, manage disease, access to care and support services, they vary widely depending on race, ethnicity, geography, and socioeconomic status. These barriers we know contribute to the health disparities, and I know you want to ensure access to these treatments that give hope and will lead people to seek early detection and diagnosis.

Why is this all relevant in the context of this new drug approval? Because, as stated earlier, last year, CMS announced it would not

cover an entire class of FDA-approved disease-modifying therapies for treatment of MCI and early dementia due to AD. This effectively cut off access to Medicare beneficiaries living with early Alzheimer's, except wealthy seniors who could pay out of pocket.

This committee is looking at the evidence on Leqembi's safety and efficacy, and I have confidence in the FDA's impartial, rigorous, and expert review, based on the merits of the phase 3 study findings. NCBA is asking not to exacerbate inequalities in Alzheimer's detection and treatment by coverage with evidence development, or CED, and layering on additional registry studies with strict requirements to site care and types of specialists after FDA traditional approval, which will only create more barriers for our communities and restrict further access to people with the highest need. I urge you to recommend traditional approval for Leqembi. Thank you.

DR. ALEXANDER: Thank you.

Speaker number 10, please unmute and turn on

your webcam. Please state your name and any organization that you're representing, for the record. You have three minutes.

MR. DWYER: Hi. I'm John Dwyer, the president of the Global Alzheimer's Platform Foundation. We are an organization that is dedicated to a patient-centric approach to improving the quality and lowering the cost of AD, Alzheimer's disease, clinical trials. I have a profound family history of the disease. Our organization conducts clinical trials in Alzheimer's disease, so as a function of that, most of our funding comes from either philanthropic groups or sponsors such as donanemab's, or Leqembi's, or aducanumab.

I want to thank the FDA for a rigorous and exhaustive process. I want to thank Eisai on behalf of the folks we work with in clinical trials, to whom we all owe a great deal as a volunteer for these initiatives and the rigor with which they have presented the data today. I call upon the committee, as you finish your process, to

please be as clear and compelling as you can be in giving guidance to the FDA because this class of drugs has been, as others have said, stricken with a large number of inflictions of uncertainty and doubt that are neither necessary nor helpful.

You have two statutes, the accelerated approval process and the traditional approval process that Congress enacted to make sure that drugs were safe and effective and decided by the science agency known as the Federal Drug Administration. We are seeing the end of that process being borne out here, and we call upon the FDA to make sure that you continue to support your statutory authority and not allow it to be eroded or confused by sister agencies who are injecting parallel or ancillary processes that do not advance the understanding of the science, in our judgment; and more importantly, are going to restrict access and delay access to these very important life-extending drugs.

It is for that reason that we think, as we move forward, that the agency, the FDA, should

incorporate, as you collaborate with CMS, whatever questions they may have, but those questions should reside within the robust statutes you execute and not new procedures, which are grounded on a statutory authority found in only three words, "reasonable and necessary." Until we can get clarity, we have seen that these drugs are clinically meaningful. They have questions around how they are administered to maintain safety, but the hard work has been done, and we encourage the FDA approve the drug, the committee to support the drug, and then let the process end there, rather than create another series of subsequent events. Thank you very much.

DR. ALEXANDER: Thank you.

Speaker 11, please unmute and turn on your webcam. Please state your name and any organization you are representing, for the record. You have three minutes.

MS. BRIDGES: I have no financial disclosures. My name is Joanne Bridges. Good afternoon. I'm with my husband, Jerome Bridges.

I'm the caregiver and he's the recipient. We've been married for 27 years. In 2015, we retired from St. Louis, Missouri to Aventura, Florida. We are a blended family of four boys and two girls who have made their homes from New York City to Seattle Washington.

As the owner of an event planning and travel company, I advised an organized domestic and international meetings, events, and vacations for corporate and leisure clients. After September 2011, the travel industry declined tremendously; therefore, I began a career as a grant writer for the St. Louis Public Library, its educational division. I volunteered to teach GED classes. I walk in the Susan J. Komen Race For the Cure. This year, I'll walk to end Alzheimer's. My primary community focus is making friends, family, and our church congregations aware that there are resources for individuals diagnosed with Alzheimer's.

Jerome was diagnosed with early onset Alzheimer's on October 28, 2019. My immediate reaction was fear, confusion, and hopelessness for

our future. I was in the process of planning fun and exciting things for our life in Florida. I was not knowledgeable about the personal impact of Alzheimer's. I thought this diagnosis would drastically change our future; instead, traveling, beaching, and spending time with our children, grandchildren, and friends was not going to happen.

Our discussion with the neurologist was very informative. He explained Alzheimer's is a progressive brain disease that destroys memory and thinking skills over time. Jerome would be an ideal candidate for inclusion in the VI and BAN2401 early Alzheimer's disease medication trial. This trial was a double-blind study. The decision was easy. Jerome would have a 50/50 chance of receiving the medication, which could slow the process of the disease or live with the debilitating effects of Alzheimer's.

I felt hopeful. Jerome was eager and looked forward to participating in the study. By receiving Leqembi, he became more talkative, smiled, was keen to help around the house, started

reading again and listening to his favorite jazz music. Jerome did not experience any adverse side effects during this study, and he is currently getting Leqembi by injection once a week at home. My day today became less stressful. We take short walks. We go to the beach, relax by the pool, dine out with friends, take weekend trips, and enjoy life. Going from hopelessness to hope for our future was made possible by Leqembi, a new lease on life.

Alzheimer's is a terrible, crippling disease for patients and their caregivers. The fact that Leqembi can slow the process is a giant step in combating the disease and making life more worthwhile for those diagnosed with Alzheimer's. Thank you for your time.

DR. ALEXANDER: Thank you for your comments.

Speaker 12, please unmute and turn on your webcam. Please state your name and any organization you're representing, for the record. You have three minutes.

DR. MARSHALL: Thank you. Good afternoon.

I am Dr. Cindy Marshall. I'm the medical director of the Baylor AT&T Memory Center in Dallas. I appreciate the opportunity to speak today. I have no financial conflict of interest.

As a dementia specialist, I've been preparing my patients for amyloid antibody therapies for some time. I was fortunate to utilize lecanemab fairly quickly. There has been a tremendous learning curve, but I'm grateful to be able to offer a disease-modifying therapy. As of today, I have 17 patients receiving infusions. The longest in treatment has received her sixth infusion. I have 5 patients who are awaiting scheduling. So far, these patients are tolerating the drug well. I have 15 additional patients who are in various stages of eligibility verification.

As others have stated, Alzheimer's is a devastating disease. My patients and families are desperate for meaningful treatment. This is my 20th year of practice, and we've been waiting a long time. The clinical data supports my use of this drug. As a full-time dementia clinician, I

strongly support traditional approval, and thank you for your time.

DR. ALEXANDER: Thank you.

Speaker 13, please unmute and turn on your webcam. Please state your name and any organization you're representing, for the record. You have three minutes.

DR. RAMACHANDRAN: Thank you. My name is Reshma Ramachandran. I'm a practicing family medicine physician and assistant professor at Yale School of Medicine, where I co-direct the collaboration for regulatory rigor, integrity, and transparency. I also serve in an unpaid position as the chair of the Doctors for America FDA Task Force. Neither Doctors for America, Yale CRRIT, nor I have any conflicts of interest and do not receive any funding from the pharmaceutical or medical device industry. My remarks today reflect my own views.

I'll be speaking today from the perspective of a prescribing clinician. Since FDA's accelerated approval of lecanemab earlier this

year, several patients and their families have asked me whether the drug could be beneficial for them and if it is safe for them to take. I had hoped that the FDA briefing documents for today's advisory committee meeting would provide clarity so that I might be able to better answer these questions; however, in reviewing these materials, I fear that I will not be able to do so. Instead, there remains several critical unanswered questions.

First, what guidance can the FDA provide to me and other prescribers on how to identify patients who are at high risk of serious adverse events or death likely due to lecanemab? I ask this because within the briefing documents, and during today's meeting, there will be discussion of possible risk factors that might further heighten the likelihood of serious harms from lecanemab. This includes cerebral amyloid angiopathy or the accumulation of amyloid plaque in the walls of arteries, which is thought to contribute to significant brain bleeding.

The FDA has acknowledged that there are no clear clinical criteria for diagnosing this, and moreoever, as also noted by the FDA, many Alzheimer's patients with this risk factor do not demonstrate characteristic findings on MRI. This means as a clinician, it will be incredibly difficult to identify patients who are at higher risk of serious harm, including death, and to be able to counsel them appropriately.

Second, will the FDA and the advisory committee elaborate on what the marginal clinical benefit seen for lecanemab in CLARITY AD means in the real world? How should we articulate to our patients whether if any meaningful clinical outcomes were seen in this trial?

Throughout the document, FDA seems to conflate clinical benefit with statistical significance. Several of my colleagues and I have struggled to understand and translate to our patients what these small changes in the cognitive score are in terms of cognitive and physical function and whether or not they're meaningful.

Third, within the CLARITY AD trial, patients under 65 do not seem to show a statistically significant benefit across all cognitive scores. Moreover, among older patients, where statistically significant change have been demonstrated in their cognitive score, they were also more likely to experience brain bleeding, brain swelling, or infusion reactions, leading to functional unblinding or awareness that they were taking the drug and dropping out of the study. Can the FDA answer whether this might have introduced bias and contributed to the differences seen between the age groups?

As a clinician, I look to the FDA to provide reassurance that what I'm prescribing is meaningfully effective and safe for my patients. I want to have a treatment option for my patients suffering from this devastating disease; however, failing to provide answers to these key questions that my fellow clinicians and I have would unfairly shift the burden of uncertainty on to prescribing clinicians, patients, and their loved ones.

Based on the current level of evidence, which failed to demonstrate meaningful clinical outcomes and assurance of safety, FDA should not approve lecanemab, and to require further studies to help us determine whether the drug is truly safe and effective for our patients. Thank you.

DR. ALEXANDER: Thank you.

Speaker 14, please unmute and turn on your webcam. Please state your name and any organization you're representing, for the record. You have three minutes.

DR. PADILLA: Good afternoon. I'm Dr. Claudia Padilla, a behavioral neurologist at the Baylor Memory Center in Dallas, Texas. I've been in practice for eight years at the memory center, where I evaluate and treat individuals with cognitive changes, specifically neurodegenerative diseases, including Alzheimer's disease. My training included a neurology residency at the University of Miami Jackson Memorial Hospital and a two-year fellowship in behavioral neurology and neuropsychiatry at UCLA and the West Los Angeles VA

Medical Center. I have no financial disclosures.

Most people are aware of the devastating impact Alzheimer's disease can have on a patient and their family. There has been a desperate need for disease-targeting therapies that make a greater impact than the cognitive medications that have been used in the past 20 years. Lecanemab and other future disease-targeting therapies will make a bigger impact on a patient's disease course.

Some of my long-term patients who participated in the phase 2 clinical trial have shown good cognitive stability and quality of life. In the past two months, I have begun to prescribe lecanemab for patients presenting with mild cognitive impairment or mild dementia due to Alzheimer's disease. I hope that we will continue to work together and move forward quickly regarding development and approval of effective therapies for this disease. Time is of the essence.

It is an honor to speak on behalf of my patients, their families, and all individuals affected by this disease. I am in full support of

traditional approval. Thank you for your time.

DR. ALEXANDER: Thank you.

Speaker 15, please unmute and turn on your webcam. Please state your name and any organization you're representing, for the record. You have three minutes.

MS. BENCIVENGA: Good afternoon. I'm Patricia Bencivenga, the special projects coordinator at PharmedOut. I have no conflicts of interest to disclose. PharmedOut, an evidence-based prescribing project at Georgetown University Medical Center, urges the FDA to reject Leqembi/lecanemab for full approval. Our reasons are 3-fold. It doesn't work, it can cause serious adverse effects, and long-term, it is likely to worsen dementia.

Leqembi doesn't work. The sponsors and the patient advocacy groups they fund persist in defending the fantasy that Leqembi and its kin can prevent a patient from slipping into the most difficult stages of the disease. That assertion is based on unsubstantiated hope. The CLARITY AD

trial does not support the clinical benefit of Leqembi. While a minimal clinically meaningful difference on the cognitive test is considered to be between 1 and 2.5 points, the difference in this trial was 0.45. Remember, this was not actual improvement. This was a reported difference in the rate of decline, a difference that neither patients nor family would notice.

The lack of any actual clinical improvement may explain why the sponsors attempt to claim a disease-modifying effect. Leqembi may well modify the disease by making it worse. Serious adverse effects of Leqembi and other monoclonal antibodies for Alzheimer's include brain bleeding and swelling, euphemistically termed ARIAs. Industry paid advocacy groups and consultants minimize these toxicities by suggesting that Leqembi removes the amyloids surrounding the blood vessels in a way similar to scraping paint off of a wall; however, it acts more like a sledgehammer, taking down the wall as well as the paint.

Monoclonal antibodies weaken the integrity

of blood vessels. Three patients taking Leqembi in clinical trials died from brain bleeds. This suggests a rate of 1 to 2 deaths per 1,000 patients, and that's in the healthier than normal clinical trial population. The death rate is likely to be far higher in a general population.

In the long term, Leqembi may worsen dementia. Those who survive treatment may suffer from brain atrophy. Shrinkage in brain volume is associated with cognitive decline in Alzheimer's disease, and this process is accelerated with Leqembi. A recent systematic review and meta-analysis of accelerated brain volume loss found that 18 months on the highest trial dose of lecanemab accelerated whole brain atrophy by 28 percent and enlarged ventricles by 36 percent compared to placebo. The whole brain volume loss was 5.2 milliliters, more than a teaspoon of brain matter.

The long-term consequence of drug-induced volume loss to brain health has not been investigated, but it's reasonable to expect that

drug-induced brain shrinkage is associated with poorer cognitive outcomes. Please don't use a standard of hope to recommend full FDA approval to any drug. The confirmatory trial does not support clinical benefit of lecanemab, and the known harms certainly outweigh the alleged minimal slowing of decline for Alzheimer's patients.

Patients and their families deserve better than false hope. This committee should not accept the data presented as sufficient for proving clinical benefit. It would create an abysmal standard for future Alzheimer's drugs applying for approval. Please vote to reject this application for full approval of Leqembi. Thank you.

DR. ALEXANDER: Thank you.

Speaker 16, please unmute and turn on your webcam. Please state your name and any organization you're representing, for the record. You have three minutes.

DR. MURPHEY: Good afternoon. My name is Donna Kim Murphey with Doctors for America. I oppose approval of lecanemab and any compound in

this class of monoclonal antibodies because of safety and efficacy being unclear, and particularly for minoritized groups. I'm a neurologist and neuroscientist with experience in brain safety monitoring and in advocating for inclusion and impacted party-centered research in clinical trials. I started a public benefit company and work closely with black and immigrant family caregivers in eliminating racialized health disparities in dementia.

I'm also a support caregiver to my 95-year-old grandmother with mild dementia, and with a personal history of brain infection, I have a 31-fold risk of dementia myself. You can imagine why I desperately want to solve this devastating condition. My grandmother technically has only mild dementia by existing clinical scales, but with persecutory delusions, she has so depleted my mother, one of the kindest people that I know. She is constantly on edge and physically sick.

Many caregivers will be outlived by their loved ones with this disease. I live with mild

cognitive effects of a prior brain infection and long COVID and shudder at the burden I will create for my own children if I live to be old enough. The stories I've heard and helped patients and their families navigate are as tragic, but still I want a treatment that is safe and effective for my patients, my family, and eventually for me.

I'm alarmed at how lecanemab has been developed and by conflicts of interest that drug sponsors -- that are consultants and organizations who should be, first and foremost, informed and unbiased advocates for families -- have had in pushing for accelerated approval despite serious side effects for this drug.

Nearly one-fifth of patients on lecanemab had brain bleeding; supposedly, only 1 percent were symptomatic. That monitoring for side effects is not as careful as for the clinical endpoints; that EEG, for instance, was not used for a class of drugs known to cause visual disturbances and confusion, both of which could be caused by seizures, is an example of the lack of rigor in

assessing for dangerous off-target effects.

Then there is a question of efficacy. Statistical significance is not clinical significance, as we've heard over and over again. Quality-of-life measurements do not ask whether the degree of change matters to the patients and families. And how can I advise all families, particularly those disproportionately impacted by dementia, when serious risk and questionable benefit of therapy are an issue?

With racialized incidence of Alzheimer's and brain bleeding in black patients, and with their significant underrepresentation in this trial, I cannot as a neurologist advise this group with the lecanemab data. Also, Asian Americans comprise 7.2 percent of the population in the United States; hardly trivial and hardly included. Inclusion of international Asians, when we know so many of the risks in dementia are modifiable and context-dependent, is not a substitute.

Finally, the cost of this drug and time and money will be prohibited. Infusions and frequent

MRIs with a projected $26,000 a year cost will put this drug out of reach for many of our families. I ask that the FDA reconsider full approval of lecanemab and require that at least a registry be performed as per CMS recommendations for accountable postmarket monitoring. Thank you.

DR. ALEXANDER: Thank you.

Speaker 17, please unmute and turn on your webcam. Please state your name and any organization you're representing, for the record. You have three minutes.

MS. MONKS: Good afternoon. My name is Doreen Monks. I'm a 70-year-old retired neuroscience nurse practitioner. I currently live in Livingston, New Jersey, and I have no financial disclosures. Prior to my retirement, I was the program director for the Stroke Center at St. Barnabas Medical Center in Livingston, New Jersey, a program I'm proud to say I developed.

In 2015, I was diagnosed with dementia, but it would take over a year for the final diagnosis of early onset Alzheimer's disease. I was

blindsided. I had every intention of dying at my desk. My life was my work, my patients, and my staff. But because of the diagnosis, I was forced to retire, so on Friday, July 15th of 2016, at the age of 63, I walked out of my office for the very last time, and the world I knew and loved had ended. It was a sudden end to my old life in that I had to find a new one, and a purpose to pursue in that new life because everything I had planned on my life being, was gone.

I found that new purpose facing Alzheimer's disease head on. I made it my personal mission to bring Alzheimer's disease out of the dark corner and into the forefront because I believe the stigma attached to the disease comes from ignorance and a lack of understanding. I now spend my time speaking out on behalf of those who can no longer speak for themselves and to show them that there's a life after the Alzheimer's diagnosis, and that they have every right to expect that to be a good one.

As a neuro nerd, I follow the science,

closely working with my neurologist to understand the concept of anti-amyloid monoclonal antibodies. She and I have had very in-depth discussions as to how these drugs might help me live the life I now live for as long as I can. I live alone without prospect of a caregiver, so the promise of these drugs like Leqembi gives me the hope of a little more time to maintain the independent life I now live.

Please remember me and the many others like me out there who are waiting for your decision today. We just want the chance for a little more time to be the people we are today, tomorrow. Thank you so much for your time.

DR. ALEXANDER: Thank you.

Speaker 18, please unmute and turn on your webcam. Please state your name and any organization you're representing, for the record. You have three minutes.

MR. BOCKNEK: Good afternoon. My name is Zel Bocknek, and I was diagnosed with Alzheimer's disease four years ago. I have no financial

disclosures. My wife Gail and I have been married for 58 years. We live in Toronto, have three sons in their 50's, and 6 grandchildren. I've been active in sports my entire life, teaching high school phys-ed for 7 years, coaching football and basketball, as well as downhill skiing. I created and ran with my wife a very successful international business for 33 years. I then went on to volunteer.

We saw the Toronto Memory Program on TV, and it seemed to address my concerns about my brother, who is in the throes of dementia and could I also be affected. This led me to call Memory Program in Toronto to set up an appointment. After testing, they discovered that I, like many others, have the amyloid protein, and I was then accepted into the study. The testing was a blind study, so I was unaware that I had been on the placebo for the trial. Once it ended, however, I was offered to either stop or receive the drug lecanemab in an open-label study. I decided to participate in the study, and as of today, I have received

45 infusions of the drug, and I'm still feeling fine.

It has given me hope that nothing has changed to date. I still maintain my activities, including winter skiing. I don't do moguls or double black diamond runs anymore, but that may be because I'm about 89. I believe that this drug can offer help by either maintaining a person's present status or slow down any deterioration.

Here's my wife.

MS. BOCKNEK: Hi. I'm Gail, and I'd just like to add a real-life example of this. I just had knee replacement surgery, and most of you know that isn't pleasant, and I've been out of commission for the past week. During this time while I can't do much, Zel has been taking care of me, and he's doing chores that he's never had to do before like making the bed, doing dishes, laundry, and cooking, et cetera. We are so grateful that he can do this, and believe that lecanemab has played a big part in this.

I think people have to understand that every

person who's involved in this on a personal level has to have some kind of glimmer of hope. There are negativities, but there's so much positivity. So thank you for allowing us to share our experience. I hope that the future will hold more trials and progress, and that we can continue to benefit from this research. Thank you.

MR. BOCKNEK: Thank you.

DR. ALEXANDER: Thank you.

Speaker 19, please unmute and turn on your webcam. Please state your name and any organization you're representing, for the record. You have three minutes.

MS. LUIGGI: Good afternoon. My name is Patricia Luiggi, and I don't have any financial disclosures. Currently living in Texas, I've been married for 45 years and have three amazing children and four grandchildren. I work as a visiting nurse, and I enjoy so much, and then during my 50's came to be a chaplain, which had been my passion.

Sadly in 2018, my memory problems started

affecting my performance, and after evaluation, I was diagnosed with mild cognitive impairment. This was the present time for me because my mother and seven of her siblings died of Alzheimer's, so I knew what my future with this condition could be. But because of my Christian faith, I embraced this situation as a new challenge in my life and an opportunity to continue maturing my character.

I determined in my heart to not let this condition define me, but around September 2022, I was having memory problems on a daily basis, like getting to the kitchen and not remembering why I was there, forgetting names and events, and how to use the computer. My husband was greatly affected by this and had to make adjustments, taking care of details that I used to be in charge of at home, like cooking, remembering my appointments, and dealing with my emotional frustrations.

I went to my doctor, and she ordered the PET scan study. The results came to be positive for amyloid plaques, and I was diagnosed with early onset Alzheimer's. At that moment, my doctor

oriented me about Leqembi and started treatment two months ago without any side effects. For me, it has been so promising and given me so much help of stabilizing my condition and delaying the deterioration process. Since I started my infusions, we celebrate every single day as a gift of God and haven taken road trips and family gatherings, and learning new skills like participating in this meeting today and sharing my story with you, and some using my computer.

My family and I are very optimistic with what this treatment can be, not only for me, but also for all patients that are experiencing this disease. We believe it can bring a new promising reality filled with hope and meaning for those who are devastated by this condition, and that this date will be remembered as the one that changed the trajectory of the lives of all Alzheimer's patients. Thank you for this opportunity.

DR. ALEXANDER: Thank you.

Speaker 20, please unmute and turn on your webcam. Please state your name and any

organization you're representing, for the record. You have three minutes.

MS. WARTMAN: Good afternoon. My name is Gretchen Wartman. I am vice president for Policy and Program for the National Minority Quality Forum and director of our Institute for Equity and Health Policy and Practice. I have no personal financial conflicts of interest. The National Minority Quality Forum is a not-for-profit organization that receives non-branded programmatic support from numerous organizations, including pharmaceutical companies, the Department of Health and Human Services, other sponsors of research, and payers. NMQF is a 501(c)(3). The mission of NMQF is to reduce patient risk by assuring optimal care for all.

We appreciate this opportunity to share our perspective on whether lecanemab should be granted traditional approval. As I noted earlier, our mission is to reduce patient risk for all. Unmitigated patient risk can be measured in the incidence and prevalence of preventable morbidity

and premature mortality, in avoidable hospitalizations, and in delayed access to health services. Most egregiously perhaps, unmitigated patient risk can be measured by less than fully representational inclusion of population and patient cohorts in the creation of new science.

During this convening, data and evidence regarding Alzheimer's disease and the safety and efficacy of lecanemab have been presented by others. What is also well documented is the need for FDA-approved therapies to treat mild cognitive impairment associated with a diagnosis of Alzheimer's disease in all populations. As long documented by the U.S. Census Bureau, the American general public is rapidly diversifying. Science that enables us to identify cohort similarities by biomarker rather than by sound or appearance is a reality. NMQF is committed to eliminating the marginalizing practices of prior centuries that present and portend future risks for all patients; however, access to new therapies should not be constrained due to long-standing systemic barriers

to inclusion in clinical research. This is indeed a fine line to travel.

The National Minority Quality Forum is hopeful that the Peripheral and Central Nervous System Drugs Advisory Committee will vote to recommend traditional approval of lecanemab. We also look forward to working with FDA, CMS, and sponsors of all research to create accessible processes to document evidence for historically marginalized populations and patient cohorts. Thank you again for the opportunity to speak today.

DR. ALEXANDER: Thank you.

Speaker 21, please unmute and turn on your webcam. Please state your name and any organization you are representing for the record. You have three minutes.

MR. LEFF: Hi.

MS. DUDA: Hi.

MR. LEFF: My name is Ira Leff, and I'm here with my life partner, Mary Duda. I am 74 years of age, and Mary is 67. We have been together for 15 years and live in New Fairfield, Connecticut

with our cool cat, Huxley [ph]. Mary was diagnosed with early onset Alzheimer's back in late 2018 by Dr. Armand Fesharaki, a neuropsychiatrist at Yale New Haven Hospital. The diagnosis was devastating for both of us, yet we did our best to deal with that reality and to maintain a positive attitude, exercise, and eat healthy.

In the autumn of 2019, Dr. Fesharaki referred us to Dr. Christopher van Dyck of the Alzheimer's Disease Research Unit at Yale New Haven, and Mary qualified and soon became a participant in his lecanemab trial study program. Mary's first infusion was in January of 2020, and soon after that, the COVID-19 pandemic arrived, and wasn't that fun for all of us. Anyway, we have recently been made aware that Mary was in the placebo group during that time and would remain so until she started receiving lecanemab during the open-label part of the trial study in August of 2021. Mary is currently still receiving infusions.

All I can tell you is this. Not long, some weeks, perhaps months, after Mary started the

lecanemab infusions, I noticed that her short-term memory abilities had improved some. She said she felt good. She was recalling recent events. She was watching TV shows and had conversations from previous days or hours.

MS. DUDA: Growing tomatoes.

MR. LEFF: She still experiences difficulty from time to time coming up with names or words and continues to have difficulty calculating numbers in her head. However, Mary cognitively still has a great sense of humor and is able to do so many things effectively. She reads, makes and answers phone calls, goes shopping, and she enjoys entertainment and her gardening and time with her friends and family.

We recently met with Dr. Fesharaki, and he compared Mary's MRI imaging from 2018 with one from November of 2022. He said it was extremely promising and actually remarkable how slowly Mary's Alzheimer's disease has progressed. We truly feel that lecanemab has significantly contributed to this result. It gives us hope. We know it's not a

cure, but quality time in a person's life really matters, and slowing down the progression of this disease buys people that quality time, and that time, especially later in life, has the greatest value of all.

MS. DUDA: That's right.

MR. LEFF: Thank you very much, and we want to thank all people who are working to cure this insidious disease. Thank you for your time.

DR. ALEXANDER: Alright. Thank you.

Speaker 22, please unmute and turn on your webcam. Please state your name and any organization you are representing, for the record. You have three minutes.

(No response.)

DR. ALEXANDER: Do we have speaker 22? There you are. Unmute, and you can start, please. You're on mute.

MS. GARCIA: Okay. Is that better?

DR. ALEXANDER: That's much better. Please go ahead.

MS. GARCIA: Okay. Thank you.

My name is Myra Garcia. Thank you so much for the opportunity to speak today. As an individual living with early-onset Alzheimer's disease, I am grateful for the Food and Drug Administration and this committee's diligence in evaluating the safety and efficacy of this much needed treatment. I've always prided myself on being someone who follows through on a task in front of me, raising my sons, performing at Carnegie Hall, and conducting major fundraising campaigns, and while my diagnosis took away my dream job as a college vice president and my ability to work at all, it has not changed my mindset.

To be with you today to encourage your full approval of lecanemab is not only an honor but an opportunity in the face of Alzheimer's disease. It was a grueling frustrating eight years to get a proper and correct diagnosis, the same diagnosis as two of my aunts. I knew that what would be in store for me, and for my family and their experiences, was going to be difficult and that

something had to change. The path was to enroll in a clinical trial.

As a proud participant, please know how optimistic I am about the future of this field. I'm grateful to be part of the process that will help others. While the thought of a cure for Alzheimer's is certainly part of my optimism, I'd like you to know that, for me, more time is enough for now, and that is the promise of treatments like lecanemab.

My diagnosis helped me reprioritize my life and made clear what is most meaningful: remaining independent for as long as possible; having more time to travel; meeting my future grandchildren; singing in my church choir. It is volunteering at a memory care center and singing with and for them. They have become my people. I see these individuals week after week, and yet they don't remember me. I am humbled knowing that I share this fate, but with treatments that can slow my decline, I can make their lives a little brighter. I can share my joy through song. I can serve.

I ask for more time not only to enjoy my family, friends, and community, but to continue to give to them. Full approval of this treatment can smooth the path for others in the pipeline, giving time and hope to thousands of people. Thank you so very much.

DR. ALEXANDER: Thank you.

The open public hearing portion of this meeting has now concluded and we will no longer take comments from the audience. We will take a quick break. Panel members, please remember that there should be no chatting or discussion of the meetings topics with other panel members during the break. We will resume at 3:20 p.m. Eastern Time.

(Whereupon, at 3:10 p.m., a recess was taken, and meeting resumed at 3:20 p.m.)

Clarifying Questions (continued)

DR. ALEXANDER: Okay. We have some additional time, so let me ask committee members if they have any additional clarifying questions for either Eisai or FDA.

Dr. Cudkowicz?

DR. CUDKOWICZ: Hi. Merit Cudkowicz. Mass General. I'm sorry to bring this question back up, but this is for the FDA. I still wanted to know the clarification of warning versus lack of knowledge around use of this drug in people on anticoagulants, as well as maybe the homozygous carriers in the CAA.

I'd like to -- physicians having the chance to have a conversation about risks with their patients and tailoring this a little, but I wonder what options the FDA has about collecting data so that it's not always an unknown. I don't know if that's appropriate for this discussion, but I think it might help.

DR. BURACCHIO: Let me see. We have postmarketing safety surveillance that is ongoing after a drug is approved, which we currently have going on with lecanemab under the accelerated approval, and that they're required to submit regular reports, expedited reports, of serious events, and then collected data regularly under the postmarketing surveillance requirements that are

regulated.

We also know that there are registries. Some are ongoing like the ALZ-NET, which is currently listed in the label for lecanemab and aducanumab under patient information; that a registry like that is available. And as more registries become available, we would update labeling to include those as needed.

Maybe I will turn this over to the sponsor to ask what specific plans they may have for collecting additional data to help inform some of these uncertainties that we have.

DR. KRAMER: Yes. Can you hear me?

DR. BURACCHIO: Yes.

DR. KRAMER: Yes. Let me ask our head of pharmacovigilance, Dr. Surick, to comment on that.

DR. SURICK: Hello. Dr. Ilona Surick, senior vice president, International Product Safety at Eisai. Thank you. The FDA already described most of the regular activities that we undertake to understand more about the safety of a product postmarketing. In addition, I believe we spoke

earlier about the open-label extension study, which of course will give us additional information on safety. It already has and will continue to do so going forward.

The enhanced pharmacovigilance really means that we actively go out and seek additional information with questionnaires for patients who have an event like ARIA. Somebody had mentioned earlier we'll look for what we can find out about the baseline MRI and subsequently; so those kind of activities. In addition to that, we'll gather information from whatever publicly available information. As the drug gets marketed further, we'll look to do some data-based studies as well.

DR. CUDKOWICZ: Thank you very much.

DR. KRAMER: Let me add to that just a little bit. This is Lynn Kramer again. We also have ongoing studies, four of them, with the IV formulation. The open-label extension for the 201 study continues. The 301 study open-label extension continues. In addition, in that study there's subcutaneous dosing that's going on, as you

heard from one of the speakers in the previous session, once-a-week dosing that person referred to.

We also have the AHEAD 3-45 study, which is a large study, 1400 patients in preclinical Alzheimer's disease, and then we have the DIAN-TU study out of Wash U. Lon Schneider is the PI on that, and that's a combination with our anti-tau antibody. We also were developing this subcutaneous, as I said, and we have additional studies there. So there are postmarketing and development studies ongoing.

DR. CUDKOWICZ: Thank you.

Questions to the Committee and Discussion

DR. ALEXANDER: Okay. 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'll now proceed with the questions to the committee and panel discussions. I would like to remind public observers that while this meeting is open for public observation, public attendees may

not participate, except at the specific request of the panel. After I read each question, we'll pause for any questions or comments concerning its wording. We'll proceed with our first question, which is a discussion question, so I'll read the question here.

Discuss the results from Study 301, CLARITY AD, and whether they provide evidence of clinical benefit of lecanemab for the treatment of Alzheimer's disease.

Let me ask members of the committee if they have any issues or questions about the wording of this question.

(No response.)

DR. ALEXANDER: Okay. Hearing none, we'll open up this item for discussion. If I can ask my fellow advisory committee members to turn on their camera for this part so we might facilitate discussion a little bit. It's a small group, but let's start with Dr. Cudkowicz, and you can give your thoughts on the evidence of clinical benefit.

DR. CUDKOWICZ: Yes. I thought the evidence

for a clinical benefit was very clear and very robust. As you can see, most of our questions were more around the safety and the subgroups, but this was robust on the primary and all the key secondaries. I was also impressed that the effect was seen relatively early, 6 months, and then it seemed to get bigger with time. That made both clinical sense, as well as biological sense, so I didn't really have any doubt around the efficacy.

The meaningfulness, I think we really heard from some of the experts and also some of the patient voices, and I think for an illness like this, where they don't have very much, these are meaningful changes for people living with Alzheimer's. A couple more months at a higher functioning state is clinically meaningful.

DR. ALEXANDER: Thanks.

Dr. Follmann, your thoughts?

DR. FOLLMANN: Yes. I pretty much agree. I thought the results were meaningful and strongly significant. I thought they were consistent. When I was reading this, I thought, what does 0.5 mean?

That's the difference of 18 months between the two groups, but the sponsor and the FDA agree this is meaningful. They give examples of what it meant to change a half of point, and going from independent function to loss of independent function, that was meaningful to me.

I thought an analysis that had been talked about a bit was important. I just wanted to stress the delay to 18 months versus 12 months -- or whatever level -- it took you 12 months to achieve on placebo, and on treatment, it took 18 months to get that. So it's like a 6-month delay of whatever that level was. I thought that was probably, for me, the most meaningful.

A final comment, I guess there's been discussion out in the community and so on of whether this is meaningful or not, and I would say in the cardiovascular world, there's a method called win-ratio analysis, where you take a person on treatment and a person on placebo, and the person on treatment has a 1-point or greater score at 18 months that counts as a win for treatment.

You can calculate the treatment wins and treatment losses, make a ratio, and then that might be a more meaningful way, or a complementary way I guess, to get at the importance of this effect. So anyway, those are the points I wanted to make.

DR. ALEXANDER: Thanks for that, Dr. Follmann.

Dr. Simuni, your thoughts?

DR. SIMUNI: Yes. I absolutely agree with what Dr. Cudkowicz and Dr. Follmann expressed. I don't think that anyone will argue that Study 301 has met its prespecified primary endpoint that is a combination of cognitive measure and function, so by the virtue of the nature of the endpoint, it is clinically meaningful, and key secondary endpoints, inclusive of biological endpoint and the number of the clinical measures, reflecting both cognition, function, and caregiver work.

The question that everyone is struggling is in the discussions, both from the professional community and some of the patient community, is what is the clinical meaningfulness of an

absolutely small delta, but I do think that it has to be put in the context of very early stage of the disease, small delta progression in the placebo arm, so the ceiling effect. And I, similar to Dr. Follmann, found very relevant additional data presented by Dr. Cohen, demonstrating time to progression to the next point; so the milestone based analysis.

So in summary, I believe the study was designed as the definitive efficacy study. The endpoints were selected to reflect if they were positive, the meaningfulness of the endpoint, and the study is positive, supporting the clinical benefit.

DR. ALEXANDER: Thanks, Dr. Simuni.

Dr. Gold? Comments?

DR. GOLD: Kudos to the sponsor and patients participating. This is a very technically good study. There was no question it was well conducted randomization work. It would have been nice to see more diversity, but it's tough to do these studies, and certainly in the middle of COVID, it was very

challenging. I think technically, the study, no question in its primary and prespecified secondary, so I think there's no arguing about that it met its prespecified primary.

Again, to the discussion about effect size, I just want to go back to some of us worked on cholinesterases, where a 6-month delay in return to baseline was viewed as clinically relevant, so I don't think we should hold this to any different standard. I think 6 months around that point, which is what I think was seen, is quite reasonable. And again, for patients who have no other symptomatic therapies, a delay in progression is absolutely meaningful. If I were faced with this decision, I know which way I would like to go.

So, to me, I don't think we're debating very much. I am still concerned about the safety, and maybe that's the next question that we'll come to, Dr. Alexander, because right now it's just clinical benefit.

DR. ALEXANDER: Yes, now we're just discussing the clinical benefit.

DR. GOLD: Yes. So from that end, I concur with most of the comments that there's no real debate in my head that this demonstrated clinical benefit.

DR. ALEXANDER: Thank you, Dr. Gold.

Ms. Johnston, your thoughts?

MS. JOHNSTON: Yes. I don't want to have to repeat what everybody said, but I do concur from the standpoint that it has clinical benefit, obviously. As a patient advocate, I have to step back 10 years when I was the primary caregiver for my father, and even with the risk, and there are significant concerns there, I can't tell you what I would have paid to have had this option. So from the clinical benefit standpoint, I'm good.

DR. ALEXANDER: Thanks.

Dr. Romero?

DR. ROMERO: Thank you. I do agree with what has been said. I just would like to add a couple points. First, I hope to not conflate the concepts of clinical meaningfulness, with statistical significance, and with clinically

important differences. This is three different things. In terms of the clinical meaningfulness of the endpoints, I think we heard from the FDA, and there's a consensus in the group that the endpoints are clinically meaningful. We also heard that according to the voice of the patients, their experience has been meaningful.

Now, we have statistically significant differences between the groups in the primary endpoints, which is the main measure of benefit that has been demonstrated in the study, but also it shows disease modification, something that Dr. Gold pointed out, the symptomatic treatments of the past. Now we're moving into a new era, but I would draw caution as to not get hung up on defining clinically important differences with only one study. This area requires way more information and a lot more data, and we're just not there as a field, but I agree fundamentally with what the panel has said. Thank you.

DR. ALEXANDER: Thanks, Dr. Romero.

I'll give my thoughts. I agree with what

the members have said so far. I think it's clearly an adequate and well-controlled study, and very robust outcomes with respect to the primary and the secondary endpoints. I think Dr. Simuni makes an important point that it's true that the CDR sum of boxes ranges up to 18, but it's important to look at the observed decline in the placebo group over the 18-month period, which was on the order of 1.6, so it's not realistic to expect a 1-and-a-half point difference given that small change over time.

So I think, overall, they've demonstrated clearly that this is an effective treatment in the population as it was defined.

Let me just go back to the committee to see if there's any additional thoughts or comments that anyone would like to make about this discussion item, and just jump in if you have something to say.

DR. GOLD: Dr. Alexander, it's Mike Gold here. Just for, I guess, ease of communication, I think when we talk about absolute changes or relative changes, again, I look for standardized

effect sizes, and I also look for number needed to treat versus number needed to harm. I think at some point, if those numbers are there, it would help us to contextualize this because it actually helps to put the benefit-risk proposition straight on the radar screen.

DR. ALEXANDER: Dr. Romero, you want to make a comment?

DR. ROMERO: Yes. Numbers needed to treat and numbers needed to harm are useful epidemiological metrics, but they require that the primary endpoints of the metric be binary, and I think we're at a stage where we need to look at the continuous signal in the endpoints at hand. So even though those are epidemiologically relevant metrics, I'm not completely convinced that we're at that stage at this point; and back to the question at hand, for the design of the trial and the endpoints that were measured, the evidence is there.

DR. ALEXANDER: Okay.

Any other comments anyone wants to make?

(No response.)

DR. ALEXANDER: So if I could summarize the comments from the advisory committee so far, I think there seems to be what I would say is strong support that the CLARITY study demonstrated a clinical benefit of lecanemab.

So we'll move on to the next question, which is a voting question. Dr. Jessica Seo will provide instructions for the voting.

DR. SEO: Thank you, Dr. Alexander.

This is Jessica Seo, DFO. Question 2 is a voting question. Voting members will use the Zoom platform to submit their vote for this meeting. If you are not a voting member, you will be moved to a breakout room while we conduct the vote. After the chairperson reads the voting question into the record and all questions and discussion regarding the wording of the vote question are complete, we will announce that voting will begin.

A voting window 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. 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 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. Voting members 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. ALEXANDER: Okay. Let me just read the question.

Do the results of Study 301, CLARITY AD,

verify the clinical benefit of lecanemab for the treatment of AD?

Are there any issues or questions related to the wording of the question?

(No response.)

DR. ALEXANDER: If there are no further questions or comments concerning the wording of the question, we will now begin the voting on question 2.

(Voting.)

DR. SEO: [Inaudible] -- zero noes and zero abstentions.

DR. ALEXANDER: Are we going to display the actual vote?

DR. SEO: I apologize, Dr. Alexander. One moment, please. We're working to resume our connection and display the results.

(Pause.)

DR. SEO: Voting has closed and is now complete. The voting results will be displayed. There were 6 yeses, zero noes, and zero abstentions.

DR. ALEXANDER: Okay. Thank you.

We'll now go down the list and have everyone who voted state their name and their vote into the record. You may also include the rationale for your vote.

We'll start with Dr. Cudkowicz.

DR. CUDKOWICZ: Merit Cudkowicz, Mass General. I voted yes. I thought the results were robust on the primary and the secondaries.

DR. ALEXANDER: Thank you.

Dr. Follmann?

DR. FOLLMANN: Yes. Dean Follmann from NIAID. I voted yes for reasons I gave during the discussion.

DR. ALEXANDER: Thank you.

Dr. Simuni?

DR. SIMUNI: Tanya Simuni, Northwestern University, Chicago. I voted yes for the reasons that I communicated in the discussion.

DR. ALEXANDER: Thank you.

Ms. Johnston?

MS. JOHNSTON: Colette Johnston, patient

representative. I voted yes. As a patient representative, I felt like this had a meaningful and significant endpoint.

DR. ALEXANDER: Thank you.

Dr. Romero, please state your name and your vote.

DR. ROMERO: Klaus Romero, Critical Path Institute. I voted yes for the reasons outlined in light of the nature of the evidence presented.

DR. ALEXANDER: Thank you.

This is Robert Alexander. I also voted yes. I thought the study clearly demonstrated the clinical benefit, as we discussed.

We'll now move on to question 3, which is also a discussion question. Let me just read this.

Discuss the overall benefit-risk assessment of lecanemab for the treatment of AD. Additionally, consider the following subgroups in your assessment: Apolipoprotein E, APOE4, for homozygotes; patients requiring concomitant treatment with anticoagulant agents; and finally, patients with cerebral amyloid angiopathy.

Are there any concerns about how this is written or the wording of this item?

(No response.)

DR. ALEXANDER: Okay. Why don't we start with that first sentence, the overall benefit-risk assessment of lecanemab for the treatment of AD.

I'll start with Dr. Cudkowicz. How about you? You can start on that.

DR. CUDKOWICZ: The overall benefit-risk was in favor, while there were some side effects that were more common, the ones we're going to talk about a little bit more, infusion and ARIA, immune H; overall, tolerability, there were a number of people that were able to stay on treatment, and it was similar given the unmet need; that risk-benefit overall seemed favorable for having this on the market.

DR. ALEXANDER: Ms. Johnston, your thoughts on the overall risk-benefit assessment?

MS. JOHNSTON: Obviously, there are some specific groups that are going to have more concerns, and I think those will be addressed with

their clinicians. But basically, the overall risk-benefit I felt was very positive. Every day of an Alzheimer's patient's life or their caregiver is just an endless series of making risk-benefit ratios, so in that position, this would be an easy one for me.

DR. ALEXANDER: Thanks.

Dr. Follmann?

DR. FOLLMANN: I talked about the benefit earlier. The risk, I focused more on the clinical risk, so the symptomatic and asymptomatic area I didn't pay so much attention to. In terms of deaths or serious AEs, the groups are quite similar. In terms of serious ARIA, there was this imbalance favoring placebo, but overall they were pretty rare. So on balance, focusing on the clinically consequential risks, I thought overall there was a strong favorable -- for the monoclonal, and was pretty clear I thought.

DR. ALEXANDER: Thanks.

Dr. Romero, your thoughts?

DR. ROMERO: Yes. Thank you. About the

homozygotes, I think --

DR. ALEXANDER: We're just talking about the overall risk-benefit. We'll get to the homozygotes.

DR. ROMERO: So the overall risk-benefit in context of the three points below, I think the overall message is there's still uncertainty in which direction things will go. And to that end, I think the value of the extension, the open-label extension, and additional real-world data sources are going to be valuable to provide additional answers there. But I think in terms of the benefit-risk, the evidence presented and the nature of the data are compelling about the benefit.

DR. ALEXANDER: Thanks.

Dr. Simuni?

DR. SIMUNI: Yes. I don't have much to add. I think that we need to be very clear, as Dr. Alexander has done. Separately, I think the two sentences in the introductory statement, in regard to the discussion of the overall benefit-risk and the population recruited in the

study, I believe that the benefit versus risks are beneficial, acceptable, and in line with a class of therapeutics, especially considering the burden of the disease and progressive nature of the disease.

DR. ALEXANDER: Dr. Gold?

DR. GOLD: Yes. I think on an overall level, I think the benefit looks quite acceptable. Two cautions, or point one, is I know that we all as physicians try to protect our patients, but I just want to guard against any journalism. Patients should be informed about the risks, and then it's their decision whether they want to take it or not. And for some patients, there's a higher tolerance of risk than for other patients. For those of us who work in [indiscernible] know this story a little bit; we know it very, very well.

The other part is just to be mindful that these studies were done under very carefully controlled circumstances in a carefully selected population. I think it was remarkable and, again, kudos to the sponsor that they allowed a broad range of comorbidities. Other studies have been

much more strict, and some have had nasty surprises in terms of what happens later on. But I think the population here generally represents the technical morbid conditions that we're likely to see in patients in the age bracket, so my sense is that there shouldn't be any surprises overall.

DR. ALEXANDER: Thanks.

Just to give my thoughts, I think the overall benefit-risk assessment is favorable, the reasons that we've discussed. I mean, there are adverse events associated with lecanemab treatment. Some of them can be quite serious, but they're monitorable. And we didn't really discuss it, but there's a treatment center available, though I think it's still an evolving area for severe ARIA or infusion reactions. I think the benefit side is clear so, again, I think the overall risk-benefit is favorable.

On this item, the overall risk-benefit, let me just ask if anyone has any additional comments. Just jump in if you have something to say.

DR. CUDKOWICZ: I'll build on what you just

said, or the comment that this was in a very well-controlled study and that this was really well managed. I do think that's going to be an important part of how this comes to a bigger population. It's going to be one that's going to take the involvement of teams and imaging. So we might see more risks as it goes outside of that controlled setting, but hopefully that will be something that can be monitored. And I'm sure people will write about it and help figure out how to do it in the best way.

DR. ALEXANDER: Okay.

Any other comments?

(No response.)

DR. ALEXANDER: Well, let's move on to the consideration of the APOE4 homozygotes, in some ways the most challenging part of this discussion.

Why don't we start with Dr. Follmann; your thoughts on this specific subgroup.

DR. FOLLMANN: Yes. For this specific subgroup, I noticed for the primary endpoint, it seemed to be a little different from the other

groups, the heterozygotes and the noncarriers, and I asked about that interaction. But I think on balance, when you look at the other secondary endpoints and so on, you don't really see a concern that they are really all that different from the other ones in terms of benefit.

Also, this was not one of the strata, so it's drilling down further. The further you drill down, the more likely you are to see things that look off, so on balance, I didn't have a large concern about the risk-benefit difference for this subgroup.

DR. ALEXANDER: Dr. Simuni, your thoughts on APOE?

DR. SIMUNI: Absolutely. I absolutely agree with you that this is probably where these three bullet points, and specifically the first one, will require most of the discussion. We need to remind ourselves that we are advising not in the newer profile [indiscernible], but the revision to the existing profile. There is a language in the current USPI specifying the warnings and

precautions with a section on APOE, and the current language says -- and I'm, to a certain degree, repeating myself in the questions that I've asked earlier

The current language is, "on-site testing for APOE4 status to inform the risk of developing ARIA." And again, in my opinion, the data that came out from 301 justifies and warrants the transition from consider testing for APOE to the revision of the language; "testing for APOE4 status is required to inform decision making and risk-benefit counseling for the patients and informing the healthcare community."

DR. ALEXANDER: Thanks, Dr. Simuni.

Dr. Cudkowicz?

DR. CUDKOWICZ: Merit Cudkowicz, Mass General. I agree completely with what Dr. Simuni just said. I do think that there's evidence that this drug works in this subpopulation. It's a small number, it's only 16 percent, but at least all the secondaries went in that direction, the exploratory quality-of-life scales, and

mechanistically it makes sense in that group. But the risks were higher in this group, not just in the placebo -- and more in the treated group, but also in the placebo group. So as physicians, I think you'd want to know the status of your patient on this and have the chance to go over the risks and benefits in more detail with the patients, and you might change your monitoring for that group as well.

So I think it is imperative to know that APOE4 status. Whether we can require it or not, I don't know. That might be a legal FDA thing, but I think it should be strongly recommended.

DR. ALEXANDER: Thanks.

Dr. Romero?

DR. ROMERO: As I was saying, considering the three points to the larger question, this one about the homozygotes, to me, just underscores the fact that there is underlying uncertainty in the underlying progression and other sources of variability that help explain what is the underlying disease progression in that

subpopulation, which happens to be quite small.

So the nature of the analysis, as Dr. Follmann was saying, is the primaries were met. You start digging and you start identifying things that are valuable to bring out to light but, to me, that's more a question of a learning paradigm for future studies to start also considering additional insights to try to find out what are those sources of variability in the underlying disease progression of that subgroup, and then be able to ascertain how to tease out any potential drug effects.

DR. ALEXANDER: Who haven't I heard from?

Ms. Johnston?

MS. JOHNSTON: Yes, I concur, especially with Dr. Simuni, that this needs to be explained. As a patient representative, the eternal optimist, the clinician is going to take the time to explain it and the patient and the caregivers are going to really reach in there and educate themselves. I think if both parties come to the table and do what they're supposed to do, it's such a small group,

and I think if we could maybe change the word or take out the word "consider" and have them do it, but all in all, I'm ok with it.

DR. ALEXANDER: Dr. Gold?

DR. GOLD: Yes. So we're not talking about the fact that the study was not done in APOE for homozygotes, but the stratification was on carrier status versus noncarrier. So the homozygote, this is a subgroup, so there's a randomization issue. But nonetheless, even though it's a small group, the actual numbers of subjects or homozygotes were not insignificant in this group, and I thought the ARIA rate was pretty striking.

If you have this discussion about benefit-risk, and the risk is really informed by your gene status, I would say it's important to figure out what you carry, but it does not only have implications with the patients, it also has implications with the family and children, so we need to be thoughtful about this.

Now, the other part that I tried to get to earlier in the discussion is that APOE4 is not just

related to plaque deposition but it ties in directly to cerebral and amyloid angiopathy, and that's a known risk factor for CAA, and it's a known risk factor for CAARI. So I think if we have a sense, at least from the cases that came to autopsy, that there was a lot of inflammation, and they were homozygotes, this adds the notion that that gene, that inflammation about APOE4 status not only talks about your risk of ARIA, but if you are APOE4 and there's evidence of some amyloid angiopathy, that's a patient population that if I were treating, I'd be very careful about putting them on this drug.

DR. ALEXANDER: Thanks.

The current label basically says if you're an APOE4 carrier, you have a heightened vigilance. There's a warning related to it, but the monitoring schedule and the dose regimen is the same. So I just wondered if anyone had any advice to FDA around that point. Is there anything you've seen in the CLARITY study that would cause you to recommend a different approach?

DR. CUDKOWICZ: The reft [indiscernible] of when they occur, are pretty similar in this group and the other two groups, so I'm not sure that the frequency of imaging would need to be changed there. Again, it might be the vigilance you have for your patient and the calls. I know the doctors are going to be all vigilant, but this is going to be a higher risk group.

DR. ALEXANDER: Dr. Romero?

DR. ROMERO: Yes, and I agree. And there's, of course, the fact that you're radiating the patients, so the frequency of taking images not only adds to the cause, but adds to the potential burden, and you could end up introducing harm unwittingly, so I would use caution in that direction.

DR. ALEXANDER: Okay.

Any other thoughts on this specific subgroup of APOE4 homozygotes?

DR. GOLD: Yes, just a quick comment. It's not uncommon in clinical trials to actually have a phone call to the subjects after some interventions

to see how things are going. It doesn't necessarily mean they need to come back to clinic, but if you wait for a spontaneous report of a headache or change in implementation, things may be far along. So it may not be unreasonable to sit there and say we're going to ask the clinic, or whoever somebody is treating, a week after the infusion or whatever, to call and make sure they're okay in lieu of bringing somebody, and then imaging over and over and over, which I agree with Dr. Romero is not practical.

DR. ALEXANDER: Any other thoughts anyone has? Otherwise, we can move on to the next category, which is patients requiring concomitant treatment with anticoagulant agents.

Who would like to start?

DR. SIMUNI: I can start. So again, looking at the current package insert, it specifies that treatment with Leqembi should be initiated in patients with mild cognitive impairment or mild dementia stage of disease in the population which treatment was initiated in clinical trials. So if

we follow by the book indication section of the PI, people on anticoagulants were excluded from this study. And based on the experience combined in the 301 and open-label study, there are very few cases to make any informed decision.

So from my perspective, it would be safe and wise to make use of chronic anticoagulation as exclusionary for consideration for this therapy, but I definitely want to hear other's opinion.

DR. ALEXANDER: Other thoughts on that about what Dr. Simuni was recommending? I thought, and I might have misremembered, that the ARIA rate was actually lower in subjects who had anticoagulants versus the ones that didn't.

Dr. Gold?

DR. GOLD: Yes. I wanted to split this out in the sense of people who need, for example, chronic or anticoagulation for Afib versus folks that are on either low-dose aspirin or something like that. There's one scenario that just crossed my mind as we were discussing it. Some of these folks are going to probably end up in a hospital

with a fall, or a fractured hip, or something, and require anticoagulation for a DVT or PE prevention. I know that it's not something the study could ever have talked about, but there are going to be patients who, in the middle of getting treatment, are going to be exposed to an anticoagulant.

I'm just trying to understand how that would actually be dealt with because it's short-term anticoagulation, but they need it. I just kind of raise that issue because I don't think we ever discussed it. I don't think there were any cases that were mentioned during the review.

DR. ALEXANDER: Dr. Follmann?

DR. FOLLMANN: Yes. Earlier in the day, I asked about the benefit for people on anticoagulants versus not, and they hadn't done that analysis, but I think it's fair to assume the benefit's similar for on or off anticoagulants. Then speaking to a point you made a little earlier, I think slide 50 of the sponsor's presentation showed that the anticoagulants didn't really modify the risk of ARIA. So in terms of that benefit and

that risk I just mentioned, I thought it was favorable for that group, so didn't have anything special to say beyond that. Theoretical risk, I can't really speak to, so I would leave that to others on the committee.

DR. ALEXANDER: Dr. Cudkowicz?

DR. CUDKOWICZ: Yes. I'm kind of leaning that I would not have somebody on anticoagulants on this drug, and thinking more of antithrombotics, I think they have more data on the antiplatelet use. It's just more common and some more numbers, but really no data or only a few people on anticoagulants. And the ones that were on it are the ones who had the more serious bleeds on the open label.

I think this is where waiting for additional data from the open label and from other studies might be helpful. When people come in for DVT, you have to treat them, and it might be that you just have to hold the medicine. But I think until we have actually more safety data on the use of antithrombotics on this drug, this is where I don't

think the benefit outweighs the risk of a large bleed.

DR. ALEXANDER: So you would favor not allowing people to be on anticoagulants?

DR. CUDKOWICZ: Right, yes. Antiplatelets, I was convinced by the data; it was okay, but the antithrombotics --

DR. ALEXANDER: Based on your concern about microhemorrhage primarily?

DR. CUDKOWICZ: Yes, correct.

DR. ALEXANDER: Dr. Romero?

DR. ROMERO: Yes. Thank you. I think striking a balance is what is important. One thing is the nature of the evidence presented, which has underlying uncertainty and the need for more information. That needs to be recognized in that particular instance. But if you need additional information, the important thing is something that Dr. Gold mentioned, to be very clear in the way that the individuals that are potential candidates for the therapy are informed about the therapy, because there's the individual risk tolerance

component, and then there's the clinical judgment of the treating physician that needs to face the patient in the individual case, which is outside of what you see at a population level in a clinical trial.

So striking a balance between those two pieces and keeping the do no harm principle as a key tenet needs to be thought of carefully between what the agency considers putting on a label versus what clinical practice guidelines would end up informing clinicians and patients about the uncertainties in what is known versus not known in terms of risks and concomitant medications. But to me, the fundamental question is we have uncertainty and we need more data to be able to make definite calls in one direction or another. And I would leave that, at this point, the clinical judgment and risk assessments, on the part of well-informed patients and families.

DR. ALEXANDER: Yes. Thanks for that, Dr. Romero.

I would be a little concerned about denying

this drug to people that are on anticoagulants given the amount of data that we have in terms of serious hemorrhages. We're just talking about a couple subjects. So I think we have to balance that because, otherwise, they'll never have the option of this treatment.

I just wondered if other people have thoughts about that. It sounds like we have a little bit of diversity of view, with some people advocating that people on anticoagulants should not be allowed to take the drug, and others like myself thinking maybe that would be premature to have that exclusion.

Does anyone else have any thoughts about that or want to respond to that?

MS. JOHNSTON: I'd like to respond to it. As a patient, or the patient's caregiver a lot of times in this circumstance, I want the option to have that information, to talk to my doctor and the person that I'm working with, and I don't want to be denied that because it's possible there's another option in the anticoagulants. The

clinician could have more information for me. I do agree that we've got to get good solid information both to the clinician and the patient, but I don't agree with taking the option away.

DR. ALEXANDER: Thanks.

Dr. Simuni, what's your thought?

DR. SIMUNI: In my opinion, at minimum -- and again, obviously the regulatory body will make the decision about the language. It has to be clearly communicated that the clinical trials excluded participants on chronic anticoagulation. Obviously, as a number of people have said, if someone is coming with acute DVT or any other reason for anticoagulation, they need to be treated.

DR. ALEXANDER: Dr. Romero?

DR. ROMERO: Can you hear me ok?

DR. ALEXANDER: Yes.

DR. ROMERO: I would agree with you, Dr. Alexander, that in the face of uncertainty, making absolute decisions could introduce harm. The fundamental interpretation that I have in this

particular case is that this is a point of uncertainty that needs to be recognized, and making population-level decisions based on that uncertainty versus making individual patient decisions based on that uncertainty requires different types of thought processes. But making absolute calls based on uncertainty is something that I'd be nervous with, and I'll leave it at that.

DR. ALEXANDER: Okay. Thank you.

It looks like someone from Eisai wanted to make a comment.

DR. KRAMER: Yes. We just wanted to make a correction. The anticoagulants were allowed in the trial and they are allowed in the open label, and that's where we got the data from that we showed; just a minor comment there. And they still are allowed in the trial.

DR. ALEXANDER: Thanks for that clarification.

Dr. Cudkowicz, you had your hand up.

DR. CUDKOWICZ: Actually, that's what I was

going to be talking about, so my question's answered.

DR. ALEXANDER: Yes. So they weren't excluded from the CLARITY trial.

Maybe I will ask someone from FDA if the agency has a position related to TPA administration with lecanemab, based on that single case.

DR. BURACCHIO: Hi. We don't have a position on TPA per se. We do have this statement that's in the label that I still think holds about using caution. I think you're going to make an individual level choice on TPA administration.

If you've got a patient who's taking lecanemab, it will be important, when they present to an ER with a stroke, to make sure that the ER staff is aware that the patient is taking lecanemab. And if they have a small vessel stroke, a small stroke that wasn't to clinically impairing, you might take that into consideration and decide you don't want to take that risk. But I can't imagine if you had a patient with a really devastating stroke, that you wouldn't consider TPA

in that situation. I know it would be a hard choice to make but, again, that's where individual consideration comes in.

I just wanted to make a general comment that we are aware of published recommendations and publications that I think are based on good clinical judgment. There are reasonable clinical considerations when you're evaluating these patients for who you would treat and who you think would not be a good candidate for treatment but also, we don't want to be too restrictive in our labeling for the purposes I think Dr. Romero has commented on. It's hard for us to put absolutes in labeling based on trials, and we do want to allow for clinical flexibility. We do think it is very important that clinicians are able to exercise good clinical judgment when they're evaluating patients.

I can't help but think of a theoretical patient that's a 55-year-old early onset Alzheimer's disease who's otherwise healthy, and maybe they're on lecanemab, they're tolerating it well, and they develop Afib. I don't want

prescribers to feel hamstrung by our labeling that they wouldn't look at that individual patient and try to decide what's best for them. So we do want to be cautious. We are aware of the risks. We want prescribers to be aware of the risks, but we also really want to encourage good clinical judgment on an individual assessment level of a patient.

DR. ALEXANDER: Thanks.

DR. SEO: Yes. Thank you, Dr. Buracchio.

This is Jessica speaking. I apologize for the interruption. I just wanted to state for the record that was Dr. Teresa Buracchio from FDA. And just a friendly reminder to all participants in the meeting, please remember to state your name before you speak. Thank you. This helps with our transcription. Thank you.

DR. BURACCHIO: Thank you, Jessica.

DR. ALEXANDER: Thanks for that. So yes, Robert Alexander.

Any other comments around this issue about concomitant treatment with anticoagulants before we

move on to the third subgroup?

(No response.)

DR. ALEXANDER: Okay.

The final group is patients with cerebral amyloid angiopathy, and I guess I'll kick this off. I appreciate the comments from Dr. Buracchio, but there does seem to be a difference between the use guidelines that were recently published and what the label allows. I understand the FDA position, but how are we going to know what the risk is unless you expose people that have significant baseline levels? I have to say that does make me nervous because I think it's likely, based on all we know, that they could be at higher risk for an adverse event.

Let me just open it up for other people to comment on this specific group of patients with cerebral amyloid angiopathy, and also if anybody wants to comment on the challenges around diagnosis of that.

DR. FOLLMANN: I guess I'll start off. I thought there are two aspects to this one, cerebral

amyloid angiopathy, CAA, and maybe it's hard to define, and people might have it but you don't know it, and that gives you disquietude about prescribing it. But I think unless you can measure it, you can't act on it, so I don't worry so much about that consideration.

What I worry more about is the exclusion of people who had what I'll call a CAA exclusion in this trial, and then trying to recommend or allow them to be within the label for the drug going forward. I thought from first principles, you generalize the study to people who are in the study, and it's dangerous to go beyond that.

I heard the FDA's argument for why they did that, and that's an argument. I think, though, going forward, we need to learn about this group, and I think I want to learn about it better than the pharmacovigilance program I think was described where an event happens, and then you try and catch what happens in terms of information and so on, so it's not prospectively planned.

So I think if we're going to allow labeling

or if we want to learn about this group, we have to have better prospective studies that look at risk for that. One thing they could do is to combine Studies 201 and 301, and then as people enter into that exclusion criterion, see what the risk is going forward. I don't know if they'll be a lot of information there, but it's something you have the data in principle to do. On balance, I probably prefer to allow this and have a prospective evaluation rather than make it a contradiction on the label.

DR. ALEXANDER: Yes. I think you're . making an excellent point, which is it would be important to capture that baseline MRI to really understand what the risk is going forward.

Dr. Cudkowicz, I know you've thought about this a little bit.

DR. CUDKOWICZ: Yes, I agree. What makes me, again, nervous about this one is that at least people with, I guess, known CAA were really excluded or with people with a significant number of bleeds. And yes, maybe other people have some

mild version of it, but we really don't know how this drug works I guess with the more evident CAA. I also, like Dean, don't think we'll capture all the data with the current approach, and it would be far better to do a prospective study in those patients so that we would have that data, and maybe that's feasible.

But I agree. I wouldn't exclude it, but I would have some warnings around it and, obviously, leave it to the judgment of physicians in their discussion with the patients. I'd be nervous about going differently than the data that we have based on the exclusion criteria.

DR. ALEXANDER: Thanks.

Dr. Gold?

DR. GOLD: There are patients who have CAARI. They've had episodes from this kind of angiopathy, and I would say that those patients, like I said, they're likely to be overrepresented in terms of APOE. My sense is, if you have a history of CAARI, you shouldn't be put on an amyloid antibody.

The problem I'm struggling with is for a lot of patients, the CAA is silent. You're not going to know, and as far as I can tell, MRI is not particularly helpful in terms of figuring out if you've had multiple infarcts or there's a lot of white matter disease. And maybe that's one way, but there's really no way to quantify.

So in this place, I'm going to quote Dr. Romero. There's a lot of uncertainty, and I think we're going to need a lot more data. And I think careful characterization of the patients going into other trials, it's going to be important to figure out whether there's a fingerprint that helps us to figure out who's got this high cerebrovascular load. But other than the CAARI patients, I don't think we're in a place, or at least I can't think of a reasonable or logical approach that I would take to try to minimize the risk right now, other than APOE. I keep going back. Those two conditions are related.

DR. ALEXANDER: Dr. Simuni?

DR. SIMUNI: Yes. I really will second

what's just been said before. I would not advocate for exclusionary criteria, but I definitely would suggest that you have this as part of the warnings and precautions, and to communicate that definition of CAA that was used in the clinical trials. This is not going to capture all the populations, but will communicate what population we have the data on.

So that's the response to that question, and I want to apologize for misspeaking about chronic anticoagulation. I have misinterpreted. Thank you.

DR. ALEXANDER: No problem.

Dr. Romero?

DR. ROMERO: Yes. Klaus Romero here with Critical Path Institute. I mean, we're back to the same point about uncertainty. The one thing that I would add is -- and this is a point that I made before -- the epistemic need versus the ethical considerations. Doing trials to prove harm is highly problematic. Now, doing observational studies and collecting real-world data to get a

better sense of the potential risks, absolutely valid, but I think that's a bit out of scope for today's conversation, and I'll end with that.

DR. ALEXANDER: Okay.

Any other other comments about this group with cerebral amyloid angiopathy? And do people concur with Dr. Gold's recommendation?

MS. JOHNSTON: I do concur. I was just going to say quickly -- just as a matter of record, by the way, Colette Johnston, patient representative -- I think it's imperative on this one that we make sure the warnings are clear, and clean, and concise, and I think in that warning it has to be stated that this is a condition that you may not know you have or may not present itself, and then we leave it up to the clinicians, and to the patients, and the caregivers to make that decision.

DR. ALEXANDER: Okay.

Yes. And I was just referring more to the inflammatory subtype that Dr. Gold mentioned.

DR. FOLLMANN: I think this is tough. If

you have something that you can't measure, the silent CAA, and you can't act on it, it doesn't change your decision making. I guess it just makes you a little more anxious, and I guess it makes you think you'd like to define it going forward. But if it's, frankly, silent, what can you do with it?

DR. ALEXANDER: Right. It's a real challenge.

DR. GOLD: I'm sorry. It's Mike Gold here. Just to make [indiscernible], CAARI is not silent. It's clear manifestations.

DR. ALEXANDER: Any other comments about this last group?

(No response.)

DR. ALEXANDER: I guess if I could sum up what we discussed, I think, overall -- and please, jump in and correct me if you don't agree with my summary -- for the APOE4 homozygotes, I think there was a general feeling that the risk-benefit still remains favorable, especially if I'm looking across multiple endpoints.

With respect to anticoagulant agents, I

think there was a little more diversity of view. . Some people are so concerned that they would suggest excluding those patients, while others felt that that was something that we could continue to collect information about. Then finally, with respect to CAA, there was a recommendation to exclude CAARI but, in general, people were supportive including these patients but with a robust system to monitor them or a reporting system, I should say.

Is that a fair summary or does anyone have anything that they want to add to that?

(No response.)

DR. ALEXANDER: It seems like people are saying yes.

Let me ask FDA if they have any questions or things they would like the committee to comment on before we adjourn.

DR. BURACCHIO: Hi. This is Teresa Buracchio from FDA. I guess one question I wanted to get a little clarification on is regarding the CAARI, and if you think that particular entity

within CAA requires more explicit labeling considerations.

DR. ALEXANDER: Yes.

Dr. Gold, you want to speak to that?

DR. GOLD: Dr. Buracchio, it's a rare but known condition associated with spikes in anti-amyloid Abeta antibodies. These folks develop what looks like classic -- in fact that's how ARIA was initially described. You have these patients that have these areas of demyelination, swelling edema, and the ones that I described, they're floridly symptomatic with encephalopathy. They look like they have encephalitis as well, seizures, et cetera, et cetera.

So I think it's intermittent, it's chronic, it's recurrent, and if anybody has a diagnosis of CAARI, I would be very, very careful to put them on an amyloid antibody because that's, in some respects, exactly what triggers their episodes. And if the agency would like some literature on that, I'm happy to provide it. There are a fair number of papers in the public domain.

DR. BURACCHIO: Yes. We have been reading about this during our review. Our review staff has looked into this entity. I just wasn't clear if you thought that this required a more specific description in labeling as a concern.

DR. GOLD: I'm not sure that I would be more specific. I mean, if somebody has this diagnosis, if they're known to have this diagnosis, I think that would be enough for me.

DR. BURACCHIO: I understand.

DR. GOLD: Alright. Thank you.

DR. ALEXANDER: Okay.

So unless there are any other comments, before we adjourn, are there any last comments from FDA?

DR. BURACCHIO: Yes. I would just like to thank all of the panel members for your comments. They've been really helpful to us. As I said, we've struggled with some of these challenging subgroups and how to characterize them, so it's really helpful for us to hear your thoughts on this as well, and different perspectives. And we will

be taking this back and discussing it internally, and how we can best capture and reflect these discussions in our decision.

Adjournment

DR. ALEXANDER: Great.

I just want to thank the sponsor, Eisai, as well as FDA, for providing such clear and complete briefing documents. I want to thank everyone who participated in the open public hearing, especially the patients and their families, and my fellow committee members. And with that, we will adjourn the meeting. Thank you.

(Whereupon, at 4:34 p.m., the meeting was adjourned.)