FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

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

Monday, June 10, 2024

9:00 a.m. to 3:55 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

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Director

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C O N T E N T S

C O N T E N T S (continued)

P R O C E E D I N G S

(9:00 a.m.)

Call to Order

Introduction of Committee

DR. MONTINE: Good morning, and welcome. I'd first like to remind everyone to please mute your line when you're not speaking. Also, please silence your cell phones, smartphones, or any other devices if you have not done so already. For media and press, the FDA press contact is April Grant. Her email is currently displayed.

My name is Dr. Thomas Montine. I will be chairing this meeting. I will now call to order the June 10, 2024 Peripheral and Central Nervous System Drugs Advisory Committee. We'll start by going around the table and introducing ourselves, stating our names and affiliations. We'll start with the FDA to my left and go around the table.

Peter?

DR. STEIN: Yes. Dr. Peter Stein, Director of the Office of New Drugs, CDER, FDA.

DR. BURACCHIO: Teresa Buracchio, Director,

Office of Neuroscience, CDER, FDA.

DR. LEE: Paul Lee, Deputy Director, Office of Neuroscience, CDER, FDA.

DR. Sally Jo Yasuda, Deputy Director for Safety, Division of Neurology 1, FDA.

DR. KRUDYS: Kevin Krudys, Associate Director for Quantitative Sciences, the Office of Neuroscience, FDA.

DR. ERTEKIN-TANER: Nilufer Ertekin-Taner, physician and scientist, Professor of Neurology and Neuroscience at Mayo Clinic, Enterprise Chair of Neuroscience.

DR. FOLLMANN: I'm Dean Follmann, Head of Biostatistics at the National Institute of Allergy and Infectious Diseases.

DR. POSTON: Dr. Kathleen Poston, Department of Neurology, Stanford University.

DR. SEO: Jessica Seo, Designated Federal Officer, FDA.

DR. MONTINE: Tom Montine. I'm Chair of the Department of Pathology at Stanford University.

MS. JOHNSTON: Colette Johnston, patient

advocate.

MS. DOLAN: Sarah Dolan, Ambassador for Davis Phinney Foundation and Advisor for Critical Path Institute.

DR. CUDKOWICZ: Dr. Merit Cudkowicz, Chair of Neurology, Mass General Hospital, Harvard Medical School.

DR. SIMUNI: Dr. Tanya Simuni, Head of the Division of Movement Disorders, Northwestern University, Chicago.

DR. PRESS: Dr. Daniel Press, Chief of the Cognitive Neurology Unit, Beth Israel Deaconess Medical Center and Harvard Medical School.

DR. IADECOLA: Costantino Iadecola. I am the Chair of the Department of Neuroscience at Weill Cornell Medical College in New York City.

DR. CARLSSON: Cindy Carlsson. I'm Professor of Medicine in the Division of Geriatrics and Director of the Wisconsin Alzheimer's Institute at University of Wisconsin in Madison.

MR. KIRSCH: Paul Kirsch. I'm the Vice President of Regulatory Affairs at Harmony

Biosciences.

DR. MONTINE: Thank you.

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

In the spirit of the Federal Advisory Committee Act and the Government in the Sunshine Act, we ask that the advisory committee members take care that their conversations about the topic at hand take place in the open forum of the meeting. We are aware that members of the media are anxious to speak with the FDA about these proceedings; however, FDA will refrain from discussing the details of this meeting with the media until its conclusion. Also, the committee is

reminded to please refrain from discussing the meeting topic during breaks or lunch. Thank you.

Dr. Seo will read the Conflict of Interest Statement for the meeting.

Conflict of Interest Statement

DR. SEO: Thank you, Dr. Montine.

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

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

FDA has determined that members and temporary voting members of this committee are in compliance with federal ethics and conflict of interest laws. Under 18 U.S.C. Section 208, Congress has authorized FDA to grant waivers to special government employees and regular federal employees who have potential financial conflicts when it is determined that the agency's need for a special government employee's services outweighs 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 committee have been screened for potential financial conflicts of interests of their own as well as those imputed to them, including those of their spouses or minor children and, for purposes of 18 U.S.C. Section 208, their employers. These interests may include investments; consulting;

expert witness testimony; contracts, grants, CRADAs; teaching, speaking, writing; patents and royalties; and primary employment.

Today's agenda involves the discussion of biologics license application, or BLA, 761248, for donanemab solution for intravenous infusion, submitted by Eli Lilly and Company, for the treatment of early symptomatic Alzheimer's disease. This is a particular matters meeting during which specific matters related to Eli Lilly's BLA will be discussed.

Based on the agenda for today's meeting and all financial interests reported by the committee members and temporary voting members, conflict of interest waivers have been issued in accordance with 18 U.S.C. Section 208(b)(1) to Dr. Cynthia Carlsson and 18 U.S.C. Section 208(b)(3) to Dr. Daniel Press.

Dr. Carlsson's waiver involves her employer's research contracts for three studies funded by competing firms. One study is funded by Eisai, and Dr. Carlsson's employer will receive

between $1,000,000 and $2,000,000. The second study is funded by Cognition Therapeutics, and Dr. Carlsson's employer will receive between $1,000,000 and $2,000,000, including 1 percent salary support to Dr. Carlsson. The third study is under negotiation between Dr. Carlsson's employer and Bristol Myers Squibb, but is likely to include 1 percent to 5 percent in salary support to Dr. Carlsson.

Dr. Press' waiver involves his employer's research contract for one study funded by a competing firm. This study is funded by Janssen, and Dr. Press' employer receives between $100,000 and $200,000 per year.

The waivers allow these individuals to participate fully in today's deliberations. FDA's reasons for issuing the waivers are described in the waiver documents, which are posted on FDA's website on the advisory committee meeting page, which can be found at www.fda.gov, and by searching on June 10, 2024 PCNS. Copies of the waivers may also be obtained by submitting a written request to

the agency's Freedom of Information Division at 5630 Fishers Lane, Room 1035, Rockville, Maryland, 20857, or requests may be sent via fax to 301-827-9267.

To ensure transparency, we encourage all standing committee members and temporary voting members to disclose any public statements that they have made concerning the product at issue. With respect to FDA's invited industry representative, we would like to disclose that Paul Kirsch is participating in this meeting as a non-voting industry representative, acting on behalf of regulated industry. Mr. Kirsch's role at this meeting is to represent industry in general and not any particular company. Mr. Kirsch is employed by Harmony Biosciences, LLC.

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 return the floor to you, Dr. Montine.

DR. MONTINE: Thank you, Jessica.

We'll now proceed with FDA introductory remarks, starting with Dr. Buracchio.

FDA Introductory Comments - Teresa Buracchio

DR. BURACCHIO: Thank you, Dr. Montine, and welcome to our committee members and guests who are joining us for today's meeting. Today we will be discussing the biologics licensing application, or BLA, for donanemab, for the treatment of Alzheimer's disease.

Before we start today's proceedings, I would first like to thank the committee for their time and effort to review the advanced materials and join us in person today to discuss the topics under consideration for this application. I would also

like to thank the public attendees who are joining us remotely today, and especially the patients with Alzheimer's disease and their family, friends, and caregivers.

Before describing some of the issues that we will ask you to discuss today, I want to note that we have not yet made any final decisions on the approvability of this application. Our comments in the background package are preliminary. We are here today to gain the committee's input into some of the issues we have faced during our review of the donanemab application so that we may incorporate your input into our decision making. I also want to acknowledge the comments submitted to the public docket and those we will hear today during the open public hearing session. These perspectives are very valuable to us, and they will also be factored into our decision.

This is the third advisory committee meeting the agency has held to discuss a drug in the class of monoclonal antibodies that target aggregated amyloid and that are intended for the treatment of

individuals with Alzheimer's disease. Drug development for Alzheimer's disease, and other neurodegenerative diseases as well, has been invigorated by recent approvals of the amyloid targeting monoclonal antibodies; however, we are aware that there are ongoing conversations among stakeholders regarding the benefits and risks of these new therapies.

Accruing data from clinical trials of other amyloid targeted monoclonal antibodies, such as the donanemab trials that we will discuss today, bring critical new information to our understanding of the efficacy and safety of these therapies and their optimal use in patients with Alzheimer's disease.

Safety is a significant concern for these therapies. Currently approved products have a class boxed warning for amyloid-related imaging abnormalities, also referred to as ARIA, and the potential risk of intracerebral hemorrhage. These adverse reactions require close monitoring for the emergence of symptoms; surveillance with MRIs;

careful selection of patients for treatment to identify those who may be more likely to benefit and less likely to have serious outcomes; and informed discussion between prescribers and patients of the potential benefits and risks.

Given these issues, it is important to have a public discussion on the data for donanemab that will factor into the benefit-risk assessment, not only for our decision making on approval, but also for healthcare providers who would be making these benefit-risk assessments for individual patients. With this in mind, we are seeking the advisory committee's input on the overall benefit-risk assessment for donanemab in Alzheimer's disease and to understand how certain unique aspects of the clinical trial design might be handled in the real-world setting if donanemab were approved.

I will now provide some background on the development program for donanemab and the issues for discussion that bring us here today. Donanemab is a monoclonal antibody that targets an epitope present in brain amyloid plaques. It is proposed

to treat early symptomatic Alzheimer's disease and the mild cognitive impairment and mild dementia stages of the disease. The proposed dosing regimen is an intravenous infusion every 4 weeks with a dose of 700 milligrams for the first 3 doses, followed by 1400 milligrams doses thereafter. In the clinical trials of donanemab, dosing was stopped once brain amyloid plaques were reduced below a prespecified threshold level on PET imaging. The applicant has proposed that such an approach may be considered with dosing of donanemab in clinical practice.

I will now go over the recent regulatory history of this application. The applicant initially submitted a BLA in May 2022 that sought accelerated approval in early symptomatic Alzheimer's disease based on the change from baseline in brain amyloid plaques as measured by PET imaging in a phase 2 study, AACG. During our review of the application, the agency determined that AACG was an adequate and well-controlled study that demonstrated evidence of robust reduction of

brain amyloid plaques on PET imaging, a measure that may be capable of serving as a reasonably likely surrogate endpoint for some stages of Alzheimer's disease.

However, in January of 2023, the agency issued a complete response letter for the application due to an inadequate safety database at the time of the submission to characterize the long-term safety of donanemab, particularly in light of the known safety risk of ARIA. It is important to note that the requirement for an adequate database to characterize safety is the same for approvals under both the accelerated and traditional approval pathways. A few months later, in May 2023, the applicant reported positive top-line results from their phase 3 study of donanemab that you will also here referred to today as AACI, or TRAILBLAZER-2, and they quickly resubmitted their application in June 2023 to include the data from that trial.

There are three sources of data relevant to the evaluation of efficacy that we will discuss

today, Study AACG, Study AACI, and the AACI safety addendum. The FDA clinical review for this application, Dr. Krudys, will go over this table in more detail during his presentation later today, but I will just highlight a few key points.

The population in all of these studies is mild cognitive impairment or mild dementia due to Alzheimer's disease in participants with the presence of amyloid confirmed on PET imaging. The two double-blind, placebo-controlled studies were AACG, a phase 2 study that enrolled 257 participants, and AACI, a phase 3 study that enrolled 1736 participants. Both studies assessed the most identical endpoints and used dosing regimens, where treatment with donanemab was ceased based on meeting a threshold of amyloid plaque reduction on PET imaging.

Both studies used tau PET imaging as an enrichment strategy to identify participants who would be more likely to decline during the course of the study. Participants with very low or no tau were excluded from both AACI and AACG. In AACI,

participants who were excluded based on tau PET imaging were given the option to enroll in the AACI safety addendum in which they received open-label donanemab. Biomarker and safety data were collected in these participants; however, clinical efficacy outcomes were not assessed. The AACI safety addendum provides data on the pharmacodynamic effects of donanemab on these participants with mild cognitive impairment or mild dementia due to Alzheimer's disease with little or no detectable tau burden on PET imaging.

Both AACI and AACG were positive studies. AACI was a large multicenter study that demonstrated robust, clinically meaningful, and statistically significant results across the primary and secondary clinical endpoints. Results were consistent across the prespecified subgroups. AACG was a smaller randomized, placebo-controlled phase 2 study that won on the primary endpoint and showed consistent numerical trends across secondary endpoints. The magnitude of the effects across the endpoints were similar to those observed in the

AACI study; however, this was a smaller study and was not powered to adequately assess the secondary endpoints. The agency considers both studies to be adequate and well-controlled studies.

As I have mentioned, the clinical trials included some unique design elements. tau PET was used to characterize patients as having no, low, medium, or high tau. Studies AACI and AACG enrolled participants with low or medium tau burden, and AACI also enrolled those with high tau burden. This was used as an enrichment strategy to identify individuals who are more likely to progress during the 18-month period of the clinical trials.

Participants with no or very low tau burden on PET were excluded from AACI and AACG; however, in Study AACI, participants that were excluded based on no or very low tau burden were given the option to enroll in an open-label safety addendum that collected biomarker and safety information. Additionally, participants received amyloid PET imaging every 6 months during the trial, and dosing

was stopped when the amyloid burden dropped below a prespecified threshold level.

We do not consider that either of these design elements are issues that would impact the ability to approve donanemab; however, these approaches will be important to consider for labeling of the product for use if approved. We understand that these approaches were used in the research setting of a clinical trial, and there may be practical considerations for the ability to implement either of these strategies in clinical practice such as the availability of amyloid or tau PET imaging; therefore, we would like input on how or if these approaches might be used in a potential post-approval setting.

With the inclusion of data from Study AACI in the resubmission of the application, the agency considers there is an adequate safety database to assess the long-term safety of donanemab. In our review of the safety data, risks of ARIA, intracerebral hemorrhage, and infusion-related reactions were identified with donanemab.

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 fully understood, but it is hypothesized that ARIA may be related to vascular amyloid deposition and increased cerebral vascular permeability and inflammation due to clearance of amyloid beta. In the majority of cases, ARIA does not cause symptoms and is found incidentally on MRI; however, serious, life-threatening, and even fatal events have been reported in the setting of ARIA.

Intracerebral hemorrhages have been reported in clinical trials of monoclonal antibodies that target amyloid both in drug and placebo arms, and both with and without co-occurring ARIA. Overall,

it has been difficult to clearly determine whether there is a greater risk of hemorrhage with these drugs because of the small number of events and because of the background prevalence of cerebral amyloid angiopathy in patients with Alzheimer's disease, which is a risk factor for intracerebral hemorrhage; however, the agency takes these events seriously, and we will continue to collect and assess these events in order to make sure that prescribers are adequately informed about the safety of these drugs.

In Study AACI, there was also an imbalance of immortality, which included 3 deaths related to ARIA in the donanemab arm. Of note, one fatality occurred in the setting of administration of a thrombolytic therapy for focal neurologic symptoms that were suspected to be stroke but were likely due to ARIA. Dr. Branagan, our clinical safety reviewer, will further describe this case and discuss the potential strategies that the agency is considering to try to minimize the risk for patients taking this class of drugs who develop

focal neurologic symptoms due to ARIA.

Given these considerations, we seek input from the advisory committee on whether the data discussed today provide evidence for the efficacy of donanemab for the treatment of Alzheimer's disease and whether the overall benefit-risk assessment appears favorable.

I will now go over the topics that we will ask you to discuss and the questions that you will vote on. You will have the opportunity to ask questions to clarify the wording of these questions prior to their discussion later today. We will first ask you to discuss whether the available data provide evidence of effectiveness of donanemab for the treatment of Alzheimer's disease in the population enrolled in the clinical trials with mild cognitive impairment and mild dementia.

As part of this discussion, we will ask you to opine on whether the available data for donanemab supports effectiveness across the tau PET subgroups. We will then ask you to vote on if the available data show that donanemab is effective for

the treatment of Alzheimer's disease in the population enrolled in the clinical trials. As part of this vote, we remind you that we do not consider the differences in the tau PET subgroups would necessarily impact our ability to approve donanemab, but this could be potentially a consideration for labeling if donanemab is approved.

We will then ask you to discuss the dosing regimen used in the clinical trials that completed treatment based on reduction of amyloid plaques on PET imaging. We are interested in hearing your perspectives on the scientific or clinical considerations that may factor into a decision to stop or continue dosing with donanemab if approved.

We will then ask you to discuss the overall benefit-risk assessment of donanemab for the treatment of Alzheimer's disease in the population enrolled in the clinical trials with mild cognitive impairment and mild dementia, and if there are some groups of patients for whom the benefit-risk assessment appears to be more or less favorable.

We will ask you to vote on whether the benefits outweigh the risks of donanemab in the treatment of of Alzheimer's disease in the population enrolled in the clinical trials.

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 the chance to ask clarifying questions. After a short break, we will reconvene with presentations from the FDA from Dr. Kevin Krudys, Associate Director from the Office of Neuroscience and clinical efficacy reviewer for this application, and Dr. Natalie Branagan, the clinical safety reviewer for this application. You will again have a chance to ask clarifying questions.

We will then break for lunch. When we reconvene, we will have the open public hearing followed by a short break. We will end the day with the discussion topics and voting questions for the committee. Thank you again for the effort you have made in preparing for and attending this

meeting, and we look forward to the insights you will provide.

Dr. Montine, I return the proceedings to you.

DR. MONTINE: 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 industry's non-employee presenters, to advise the committee of any financial relationships that they may have with industry, such as consulting fees, travel expenses, honoraria, and interest in a sponsor, including equity interests and those based on the outcome of this meeting.

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

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

We will now proceed with the presentation from Eli Lilly and Company.

Applicant Presentation - David Hyman

DR. HYMAN: Good morning, Chair, members of the advisory committee, and members of the FDA. I'm David Hyman, Chief Medical Officer at Eli Lilly. We understand the impact Alzheimer's disease has on the daily lives of patients, their families, and the healthcare system. Recognizing the enormous burden this disease carries, we take the responsibility of bringing a well-characterized, disease-modifying therapy to patients very seriously. Given this, we value today's opportunity to discuss the data supporting donanemab's use in patients with early symptomatic Alzheimer's disease.

Based on our respective briefing books, we

believe there is significant alignment on both the key topics, as well as data interpretation between ourselves and the FDA. We hope that the discussion today will provide further reassurance to the field regarding the importance of amyloid targeting therapies, in general, and donanemab specifically for the treatment of this terrible disease.

The development of donanemab began almost 20 years ago with the discovery by Lilly scientists that anybody targeting this unique epitope could potently and selectively remove pathologic amyloid plaques. Based on this observation, we worked hard to bring donanemab through clinical testing in an efficient and informative manner. The most ambitious long-term goal of this program has been to prevent the onset of symptomatic Alzheimer's disease entirely; however, we recognize that this would require a stepwise process, starting first with treating early symptomatic disease.

Since the first participants were dosed in 2013, we've conducted two randomized studies, both of which met their primary endpoint, a first for

the field. We are excited about the opportunity donanemab offers to patients and their caregivers. At the same time, we fully recognize that this is an important but ultimately incremental step in the treatment of Alzheimer's disease. Patients deserve more, and we continue to work on additional approaches to address this disease.

Although this is beyond the scope of today's conversation, in addition to treating early symptomatic Alzheimer's disease, our next focus is on delivering the phase 3 study of donanemab in patients with Alzheimer's disease brain pathology but who have not yet developed symptoms. We call this preclinical Alzheimer's disease.

This study is fully enrolled. The goal here is bold, to prevent the development of symptomatic Alzheimer's disease. We are very excited about the potential for this approach, but while these efforts are ongoing, we are pleased to provide early symptomatic patients with another treatment option that can meaningfully slow their clinical decline and reduce the burden of this disease.

With this background in mind, here's the agenda for today's presentation. Dr. Mark Mintun will review the donanemab clinical development program, Dr. John Sims will then present clinical efficacy results, and Dr. Melissa Veenhuizen will present safety results. Finally, Dr. Reisa Sperling, from Brigham and Women's Hospital, Massachusetts General Hospital, and Professor at Harvard Medical School, will conclude with her clinical perspective. Thank you, and I'll turn the presentation to Dr. Mintun.

Applicant Presentation - Mark Mintun

DR. MINTUN: Thank you. I'm Mark Mintun, Group Vice President of Neuroscience R&D at Lilly. Alzheimer's disease is a serious age-related neurodegenerative disorder characterized by a progressive and ultimately fatal decline in cognitive and functional abilities. Every 65 seconds, someone develops Alzheimer's disease, and since 2020, Alzheimer's disease has been listed as the sixth leading cause of deaths in the U.S.

So it is no surprise that this terrible

disease impacts many, many families. In fact, one-third of Americans have a relative who has suffered or is suffering from Alzheimer's disease, and the impact extends well beyond the patient. The requirement for increased care results in increased financial, psychological, and physical stress for the patient's caregiver and family. As just one example of this impact, in 2023, caregivers of people with Alzheimer's disease provided an estimated 18.4 billion hours of unpaid assistance.

The irreversible progression of Alzheimer's disease highlights the need for a disease-modifying treatment that can slow the rate of clinical decline. The Alzheimer's disease continuum shown here includes three phases: the preclinical, mild cognitive impairment, and dementia due to Alzheimer's. The dementia phase is further subdivided by increasing levels of severity. As patients progress along the continuum, their memory and physical abilities decline at an ever increasing rate.

It is estimated that at any time, approximately half the patients diagnosed with Alzheimer's disease have early symptomatic disease, and it is this stage that was the focus of the donanemab clinical program. And while the rate of Alzheimer's disease progression varies widely for individual patients, data shows that 30 to 50 percent of those patients with mild cognitive impairment will progress to the dementia stage over a 5 to 10 year period.

So diagnosing and monitoring of Alzheimer's disease has evolved, both in clinical trial standards and in clinical practice. Clinical trials typically use measures that have been standardized to assess patients' cognition and function. Prior to the last 10 years or so, the identification and diagnosis of an AD patient for a therapeutic trial rested solely on the clinical measures; more recently, though, amyloid PET has been extensively integrated into trials with the newer tau PET biomarker augmenting the assessment of Alzheimer's disease pathology.

These two biomarkers allow for more precision in the diagnosis and staging for clinical trials; however, in clinical practice, it is the amyloid PET or CSF amyloid levels which are the primary tools used for confirmation of Alzheimer's disease pathology with the very recent emergence of plasma biomarkers.

So turning to donanemab itself, donanemab is an antibody developed to remove amyloid plaques, the key and defining feature of Alzheimer's disease. Specifically, it is an IgG1 monoclonal antibody directed at a specific modified form of Abeta that is present only in brain amyloid plaques.

Donanemab enters the brain, binds to these amyloid plaques. The presence of donanemab attracts the attention of the immune system, and the amyloid plaques are then removed through a microglial-mediated phagocytosis. By avoiding other soluble species and targeting a highly specific plaque epitope, the donanemab provides robust and rapid removal of amyloid plaque, and

this target specificity also provides the basis to recommend that the treatment with donanemab can be considered complete once the amyloid plaques are cleared.

So the proposed indication is for the treatment of Alzheimer's disease. Treatment should be initiated in patients with mild cognitive impairment or mild dementia stage of disease, the population in which treatment was initiated in the clinical trials. The proposed label will also include the need to confirm amyloid pathology prior to treatment. The proposed dosing is 700 milligrams IV every 4 weeks for the first 3 doses, titrated up to 1400 milligrams IV dosing every 4 weeks thereafter. Stopping dosing of donanemab can be considered if amyloid plaques are cleared based on PET imaging.

So we're here today because of the important need for additional disease-modifying treatments, including treatment options that offer patients and physicians less frequent infusions, the potential of limited duration treatment, and the ability to

optimize treatment to individual needs from a benefit, a risk, or a burden perspective. We will review data in today's presentation that demonstrates donanemab provides clinically meaningful and statistically significant slowing of cognitive and functional progression in patients living with Alzheimer's disease.

Donanemab met the primary and secondary endpoints across multiple studies and showed biomarker activity supportive of those clinical outcomes. The safety profile of donanemab has been well characterized over the clinical development program and the data is consistent with the known class risks. Most safety-related events are manageable with the most common events of ARIA and infusion-related reactions that can be further mitigated with additional monitoring and education, which is planned post-approval.

Let me now share the donanemab clinical trial design. Our clinical development program was designed to demonstrate benefit in patients with early symptomatic Alzheimer's disease. There are

two key studies in our program that had similar designs of donanemab dosing, clinical staging, amyloid pathology confirmation, and prospective characterization of all patients with tau PEP. The registration quality phase 2 AACG study, also known as TRAILBLAZER-ALZ, demonstrated clinical benefit, hit its primary clinical outcome, showed substantial treatment-related clearance of amyloid plaque, and also showed evidence of impact on downstream biomarkers.

The focus of today's presentation will be primarily in our phase 3 study, AACI or TRAILBLAZER-ALZ2, which assessed the efficacy and safety of donanemab in a similar but expanded population and used similar dosing as in the phase 2 program. We enrolled an addition of 1,053 patients that were amyloid positive in an addendum, which evaluated amyloid clearance, other biomarker data, and safety. Enrollment was regardless of tau pathology and included patients with no or very low tau.

So now let me take a minute to give some

background on the use of tau PET in our program. We and others have demonstrated that tau burden is prognostic of subsequent rate of clinical decline. Now, while the technology of tau PET has not yet advanced to allow reliable and reproducible quantitative measurements in routine clinical practice, in the context of a carefully controlled clinical trial with standardized scan collections and central reads, this has been successfully implemented.

In our donanemab program, we used prospective tau characterization to ensure the trial groups who are well balanced. Additionally, it ensured patients would have sufficient clinical progression during an 18-month study to allow detection of any treatment effect. For the phase 2 AACG study, we focused on enrolling a homogeneous population of low-medium tau patients. For our phase 3 program, we broaden the population to include low-medium and high tau. And finally, in our open-label addendum, we enrolled amyloid positive Alzheimer's disease patients regardless of

tau level and specifically included patients with no or very low tau.

Study AACI was the multicenter, randomized, double-blind, placebo-controlled phase 3 study, and patients were randomized 1 to 1 to receive either donanemab or placebo. Stratification criteria included investigative site and, of course, the tau levels at baseline. Patients in the donanemab group received 700 milligrams IV infusion every 4 weeks for 3 doses, and then 1400 milligrams thereafter. Patients were also followed in a long-term extension program, which is currently ongoing.

A unique feature of the AACI study was the limited duration dosing in which patients stopped donanemab treatment prior to the end of the 18-month trial based on treatment-related amyloid clearance. The sponsor, patients, and investigators continued to be blinded in these circumstances, and the patients continued only with placebo infusions for the rest of the study.

So turning to enrollment criteria, patients

between 60 and 85 years of age with early symptomatic Alzheimer's disease and an MMSE inclusion range of 20 to 28 at the time of screening were enrolled in Study AACI. The two stages of early symptomatic AD -- mild cognitive impairment and mild dementia -- correspond to stages 3 and 4, respectively, as described in the FDA draft guidance on AD clinical studies. In addition, patients were screened for brain amyloid plaque and tau pathology by PET.

We allowed various comorbidities to better evaluate possible risks of those comorbidities within a randomized-controlled trial rather than to leave this uncertainty to clinical practice. For example, the trial included patients with potential high baseline conditions such as superficial siderosis, stroke, other vascular abnormalities, and anticoagulation.

It is relevant to note that our clinical development program, including the two registration quality studies, enrolled a higher risk population than other contemporary Alzheimer's disease trials.

This included patients that were older; had higher baseline Alzheimer's disease pathology burden; were more progressed by both clinical scales and by stage of disease; could have superficial siderosis; and a larger portion were using symptomatic AD medication. We estimate that 50 percent of the population included in our phase 3 study were too clinically advanced for eligibility in other studies, highlighting the importance of more treatment options for this disease.

Moving to study endpoints, the primary endpoint was to change from baseline to week 76 using the Integrated Alzheimer's Disease Rating Scale, or IADRS, which assesses both cognition and function. We used this primary endpoint to replicate our phase 2 study. We agree with the FDA on the importance and meaningfulness of the CDR sum of boxes and made that our first gated secondary endpoint. Other key secondary endpoints are shown here, and all of these outcomes were controlled for multiplicity.

Thank you, and now I'll turn the

presentation over to Dr. John Sims to review the results of the donanemab development program.

Applicant Presentation - John Sims

DR. SIMS: Thank you, Dr. Mintun.

Hello. I am John Sims, Head of Medical Development for donanemab. It's a pleasure to present the results supporting donanemab for patients with early AD. Let's start with the demographics.

Baseline demographics were similar between placebo and donanemab. Patients were, on average, 73 years of age, mostly white, and with 70 percent prevalence of APOE ε4 carriers, and approximately 60 percent were already treated with symptomatic AD medications. Across all the clinical scales, numerical scores were also balanced between groups. Scales and biomarkers reflected a population of an advanced early symptomatic AD. Over one-third had mild AD dementia, and the average amyloid load exceeded 100 centiloids.

Let's move to trial disposition. 1736 patients were randomized across both treatment

arms. Most patients in both groups completed the study. More patients discontinued in the donanemab arm, and the reasons are in the table. The number one reason for treatment discontinuation was due to adverse events of infusion-related reactions.

Moving to the primary results, Study AACI met its primary and key secondary endpoint in the overall enrolled population. The graph on the left shows the mean change from baseline and IADRS over the time in both treatment groups. On the right, you see the CDR sum of box over time. Worsening of the disease on the Y-axis is represented downwards on both graphs. A significant and clinically relevant slowing of clinical progression for donanemab was demonstrated on both the IADRS and the CDR sum of box, 22 percent for the IADRS and 29 percent for the CDR sum of boxes at 76 weeks compared to placebo.

Statistical separation was shown as early as 12 weeks for both endpoints. Importantly, each of the components of the IADRS were also met with

strong significant statistical significance. These results were also supported by sensitivity analyses for any potential unblinding to ARIA or infusion reactions and were robust to imputations for missingness, as noted in our briefing document. These data reflect highly meaningful results for patients with early symptomatic AD, showing reductions in cognitive and functional decline.

Here, I'm showing the same results but for the low-to-medium tau population. In this population, again donanemab treatment showed highly significant outcomes for both the primary and key secondary endpoint, 35 percent for the IADRS and 36 percent for the sum of boxes, slowing at 76 weeks. As noted, tau level was a stratification factor and a prespecified analysis population, and important from the perspective of replicating the prior positive phase 2 data.

Here are the components of the CDR sum of boxes by domains assessed within the scale. These domains include such things as memory, home and hobbies, personal care, which are truly meaningful

daily measures experienced by donanemab-treated patients and reflected by their caregivers; and again, we see significant slowing with donanemab treatment on clinical progression relative to placebo across all the cognitive and functional domains. This translates into a meaningful impact on the practical aspects for people living with this disease and those that provide their support.

One of the most important outcomes that we prespecified and control for multiplicity testing is progression to the next stage of the disease. This is measured by using the CDR Global Score. The figure is similar to the figure presented earlier, only we are adding the scores that correspond to each of the stage of the disease, and moving from one stage to the next is a large decline for patients and impacts to caregivers.

To assess progression to the next stage, patients were evaluated every 3 months for changes during the trial. In order to be considered as worsening or progressing to the next stage of disease, a patient had to have two consecutive

scores greater than their own baseline.

Here, we see the results of this analysis. The percentage of patients progressing on the CDR Global Score is on the Y-axis and weeks from their first infusion is on the X-axis. As you can see, significantly more placebo patients worsened to the next stage of the disease compared to the donanemab-treated patients. This represents 37 percent lower risk of progressing to a worse stage of Alzheimer's disease with donanemab treatment.

Moving to subgroup analyses, here again we see a pattern that benefits and favors donanemab treatment demonstrated across virtually all the subgroups analyzed. Many of the subgroups included smaller sample sizes and are not powered for statistical comparison; however, the directionality of outcomes is favorable, supporting donanemab treatment, including across APOE genotypes and tau levels.

Then finally, to look at outcomes as linked to biomarkers, it is likely that the clinical

impact demonstrated in AACI by donanemab treatment is a result of the rapid and large effect of amyloid lowering, illustrated in this trial in the left graph. If we look across the AACI program, which includes the addendum, this amyloid reduction is accompanied by and linked to improvements in other downstream pathological markers of AD. As seen in the table on the right, this effect is seen across the entire tau spectrum and further supports the ability of donanemab to target amyloid irrespective of tau pathology in patients with Alzheimer's disease.

These amyloid results also support donanemab dosing recommendations. Here, we show treatment-related amyloid clearance defined as a visually negative read or as we measured quantitatively with a centiloid value of less than 24.1. On the Y-axis is the percentage of people with measures consistent with this approach of a single negative amyloid scan. This is a clinically relevant measure for individualized treatment decisions and outcome that we control for

multiplicity and that we thought could be used in the real world to guide treatment decisions.

Two-thirds of patients achieved treatment-related clearance by 52 weeks and three-fourths of patients by 76 weeks of treatment. This demonstrates that patients achieving treatment-related clearance could stop therapy to optimize benefit and risk and burden for individualized outcomes. But how did these patients do who stopped therapy?

As a reminder, patients who completed donanemab treatment remained in the study and received saline infusions in the blinded manner. Here, we are showing that patients in the donanemab arm that completed treatment during the trial at 6 or 12 months, and among those, the mean time to completion, shown in the red dotted line, is 47 weeks. These were the patients who were receiving saline infusions for the remainder of the 18 months in the study. Despite completing the treatment, there was a continued widening of difference between donanemab and placebo groups,

suggesting disease-modifying change and a clinical trajectory that might be expected to be lasting beyond the study period.

We have continued to explore the long-term implications of amyloid lowering, and within AACI, our longest data comes from those who completed dosing at 24 weeks. The graph on the left shows this group has little to no change in amyloid over a year on placebo infusions and the graph on the right illustrates amyloid levels in those that completed treatment after one year, which also doesn't change while receiving placebo infusions for 6 months.

These data, together with additional data from phase 2 with longer follow-up periods, were used to evaluate reaccumulation of amyloid, which shows reaccumulation at about 3 centiloids per year. This is a rate equivalent to the slow natural history of plaque accumulation in Alzheimer's disease and helps support or reinforces an approach of limited duration dosing following plaque clearance.

So in summary, donanemab significantly slowed cognitive and functional decline in the population enrolled in the clinical trial with MCI and mild AD dementia. Statistically significant and clinically meaningful data was consistently demonstrated across all gated cognitive and functional secondary endpoints, sensitivity analysis, and favorable treatment effects were observed across virtually all subgroups. Clearance in amyloid plaque and additional biomarkers further support the clinical benefits observed, and patients completing donanemab treatment early, based on adequate plaque clearance, continued to separate from placebo with slower decline.

Treating earlier in the symptomatic disease is supported by prespecified tau pathology analyses, but benefit from donanemab treatment is shown across all tau levels. Importantly, the results of the AACI study replicated the successful findings observed in phase 2.

Thank you. I'll now turn the presentation over to Dr. Veenhuizen to review the safety data.

Applicant Presentation - Melissa Veenhuizen

DR. VEENHUIZEN: Thank you, Dr. Sims.

Good morning. I'm Melissa Veenhuizen, Vice President of Global Patient Safety at Eli Lilly. I will now review the safety data supporting donanemab.

To most accurately characterize the safety profile of donanemab, we looked at the safety data using various analysis populations. The first is AACI, our phase 3 placebo-controlled study; the second is Dona-PC, and this is an integrated safety analysis that includes the phase 2 and phase 3 placebo-controlled studies; and finally, the All Dona population, which is the largest. This includes the donanemab-treated patients from the Dona-PC group, as well as additional donanemab-treated patients from other ongoing studies and the AACI addendum. Based on the recommended dosing regimen for donanemab, which is 3 infusions at 700 milligram with subsequent doses at 1400 milligram, we have safety data from over 1,000 patients exposed for at least 12 months and a

total of 2,802 patients with 3,470 patient-years of observation in the All Dona group. To date, this is the largest clinical trial safety data set compiled for an amyloid targeting therapy.

We also assessed the safety data using various analysis methods. Our prespecified safety analysis shows data from the first dose of donanemab through the end of the treatment period plus 57 days, which equates to approximately 5 half-lives of donanemab. This analysis approach was agreed to with the FDA and closely aligns with what other products have done in this class.

The important take-away is that regardless of analysis population or method, the safety data remains consistent with minimal differences. For today's presentation, we will focus on the integrated Dona-PC and All Dona analyses. Data from all three populations can be found in your briefing document.

Now, turning to the safety overview, based on our prespecified integrated analysis approach, the frequency of any treatment adverse event was

similar, and serious adverse events were generally comparable between groups. Discontinuations occurred more frequently in the donanemab arm mostly due to infusion-related reactions and ARIA events. A difference was observed in the number of deaths in the placebo-controlled time period, with 18, or 1.8 percent, reported in the donanemab treated group and 12, or 1.2 percent, deaths in the placebo group. This was driven mostly by 3 cases of fatal ARIA. In the All Dona group, the overall frequency of death was 1.3 percent.

The last row in this table shows mortality based upon the most recently requested FDA approach, with additional data collected regarding vital status. The updated analysis includes any death from the first dose through week 76, irrespective of whether the patient was on active treatment or had withdrawn. The numbers here reflect the integrated placebo-controlled safety data and the vital status confirmation on 90 percent of all patients in AACI. This minimizes the uncertainty on the frequency of mortality,

based on discontinuations.

This table summarizes mortality using the two different approaches. The first row shows the prespecified analysis followed by the number of deaths associated with ARIA. These three ARIA-related events were assessed by the investigator and Lilly as related to donanemab. None of the other causes of death were considered related to donanemab. Then using the recent FDA methodology, incorporating all known vital status information, mortality is 2 percent for the donanemab arm and 1.7 percent for placebo; then the frequency of deaths outside of ARIA is the same in both treatment groups at 1.7 percent.

Not shown here, there are two additional ARIA-related deaths in the open-label extension, one, ARIA-E, and one, intracerebral hemorrhage in a patient treated with a thrombolytic for stroke-like symptoms and later identified to have ARIA-E based on the central MRI. Using the updated analysis approach, these plots compare all deaths and non-ARIA deaths. The cumulative incidence of death

at 76 weeks using Kaplan-Meier methods and the Cox proportional hazards model shows a hazard ratio of 1.2 for all deaths and 1.0 for non-ARIA-related deaths.

The confidence intervals for both treatment groups overlap, and the plot of non-ARIA deaths on the right shows that beyond the 3 deaths associated with ARIA, there's no evidence of an increased risk of mortality or excess deaths related to donanemab.

To summarize mortality, the overall frequency of death was low and numerical differences in frequency were related to ARIA. Other than the three ARIA-related deaths, there was no pattern or grouping of AEs that led to death. Key learnings from the development program have informed our risk management recommendations specifically for managing ARIA, which we'll discuss in the upcoming slides. Consistent with the class, we will perform post-approval safety studies which will further characterize treatment risks, including ARIA.

Let's move on to review adverse events. For

common adverse events, ARIA was the most frequently reported event in the donanemab treatment group. Fall and headache were commonly reported in both groups and infusion-related reactions and superficial siderosis were additional events that occurred more frequently in the donanemab treatment arm compared to placebo.

Looking at adverse events of special interest, let's begin with ARIA. ARIA is a consequence of amyloid breakdown in the cerebral blood vessel walls that has also been noted with other monoclonal antibodies that target amyloid plaque. It is primarily identified using MRI. Asymptomatic ARIA-H occurs, to some extent, naturally in the Alzheimer population, whereas ARIA-E is uncommon. Across the Dona-PC and All Dona safety populations, most ARIA was asymptomatic.

As expected, donanemab-treated patients had a higher frequency of ARIA-E and ARIA-H compared to placebo, and importantly, the incidence of serious adverse events with donanemab were infrequent and

occurred in 2 percent of patients. All SAEs were symptomatic, except for one case of ARIA-H. ARIA-E that was symptomatic was observed in 6 percent of patients and ARIA-H in 1 percent. Clinical symptoms associated with symptomatic and serious ARIA often included headache and confusion, with dizziness, nausea, and seizure occurring less frequently. Most of these symptoms were mild to moderate in severity. Intracerebral hemorrhage was also noted, and it was uncommon. Although not shown on this slide, the frequency of ARIA-E or ARIA-H for donanemab-treated patients using antithrombotic medications was similar to the frequency for patients not using antithrombotic medications.

Here is the timing of serious ARIA events in the all donanemab population. The number of patients with an event is shown on the Y-axis with the number of infusions they received on the X-axis. Most patients experienced events early prior to the 6th infusion, with a decreased risk over time. In the clinical trials, the arrows show

where MRIs were originally scheduled.

Due to the timing of these serious ARIA events, we added an MRI, shown in green, prior to the second infusion in the clinical trials. Although the numbers are small, this additional MRI resulted in a 25 percent reduction in serious ARIA and a 35 percent reduction in symptomatic ARIA. This addition was not in place prior to the ARIA deaths that we discussed. The MRI prior to the second infusion can help detect ARIA earlier when it may be asymptomatic and before it becomes serious; now, the gray arrow shows where an MRI prior to the third infusion has been added in our proposed labeling to further aid in the detection of ARIA events that may become serious.

To inform, minimize, or mitigate risk associated with ARIA, we recommend a multifaceted approach. This starts with identifying patients at higher risk of ARIA prior to treatment, including a review of the APOE-4 status, if known, an evaluation of baseline MRI for presence of superficial siderosis, and the number of

microhemorrhages.

Next, we've taken the learnings from our clinical program and recommend additional MRIs in proposed labeling to target evaluation at times of greatest risk and help minimize the frequency of these events. Additionally, a standard dose titration along with interruption or discontinuation is recommended to manage treatment-emergent ARIA. Symptomatic ARIA may require further intervention such as the use of corticosteroids, and periodic re-evaluation of the evolving neuropathology is also warranted.

We also want to improve the knowledge and confidence of healthcare providers first by working with the FDA on appropriate labeling, for example, including a boxed warning similar to currently approved amyloid targeting therapies. Having a patient card available for prescribers to distribute to patients and caregivers is also anticipated. Lilly plans to educate patients and healthcare providers on identifying, monitoring, and treating ARIA in patients receiving donanemab.

We are also proposing post-approval observational studies to further characterize ARIA in donanemab-treated patients.

Now, let me briefly review infusion-related reactions and anaphylaxis. Infusion-related reactions were reported by 9 percent of donanemab-treated patients across the clinical program and was the top reason for patient discontinuation. Ninety-four percent of these were mild to moderate in severity and occurred during infusion or within the first 30 minutes.

The most common signs and symptoms of infusion-related reactions were erythema, nausea or vomiting, chills, and sweating. Ninety-eight percent of these IRRs were transient and resolved in the same day. Serious infusion-related reactions, anaphylaxis, or other hypersensitivity was uncommon; 3 or 0.3 percent of donanemab-treated patients had anaphylactic reactions reported in the placebo-controlled period. Of the patients with an IRR that were rechallenged, 60 percent did not have another infusion-related reaction.

We're proposing label language to warn of hypersensitivity to donanemab infusion and recommending that patients are monitored for at least 30 minutes post-infusion, and infusion related reactions will also be evaluated in post-approval safety studies.

In summary, the most common adverse event for donanemab was ARIA, which is consistent with the class of amyloid targeting therapies. While most cases of ARIA were asymptomatic and resolved, serious and symptomatic ARIA was observed and was uncommonly fatal. Clear labeling utilizing dose titration, including warnings outlining the potential risks and use of targeted MRI monitoring early in treatment, along with healthcare provider education and use of a patient card, will all help to inform on and manage the risk of ARIA while providing patients important amyloid clearance to slow disease progression.

Infusion-related reactions are common, as has been observed with other monoclonal antibodies. They're monitorable and most were mild to moderate

in severity. Other than ARIA, there was no increased risk of death, and post-approval studies will further characterize the uncommon to rare risks that may be associated with donanemab treatment. The potential risk of donanemab can be managed through our proposed labeling and risk management approaches, resulting in an overall positive benefit-risk balance.

Thank you. I will now turn the presentation to Dr. Sperling to provide her clinical perspective.

Applicant Presentation - Reisa Sperling

DR. SPERLING: Good morning. I'm Reisa Sperling. I'm a neurologist and a clinical investigator from Boston, and I appreciate the opportunity to provide my perspective on the clinical use of donanemab. I want to begin by addressing my disclosures. I have consulted for a number of companies developing treatments for Alzheimer's disease over the past three years, all below the 5,000 NIH guidelines. I paid for my own travel to come here today. I do want to

acknowledge that I was the co-leader of an NIH-funded public-private partnership trial that tested a different antibody made by Eli Lilly in the A4 study in preclinical Alzheimer's disease or stage 1-2 Alzheimer's disease.

I want to begin by getting us back to what I believe is one of the most pressing unmet medical needs facing our country, and that is finding successful treatments for Alzheimer's disease. Alzheimer's disease is the most common etiology that contributes to late-life dementia, and the prevalence increases exponentially by decade. And because we're doing such a good job at keeping people alive longer, we are creating a public health emergency if we don't find a way to stave off this disease.

It's now estimated that one out of every three seniors will die with dementia, and that is more than the mortality of breast cancer and prostate cancer combined mortality in this age group. The good news is that we can now detect and monitor the pathophysiologic process of Alzheimer's

disease during life, and we can reliably and substantially decrease amyloid plaque buildup with biologically active treatments, and we can slow the cognitive and functional decline if treatment is started at least at the early symptomatic stages of Alzheimer's disease, and I greatly hope one day soon before the symptoms of Alzheimer's disease are apparent.

I was very gratified to be able to see the donanemab data in its entirety now. Here, I'm showing you the summary from the primary publication in JAMA last summer, which again on the left shows the dramatic decrease on amyloid PET with donanemab treatment and the association with, in my opinion, very consistent results, consistent across all the timepoints, consistent across multiple outcomes, and consistent across the multiple groups evaluated.

So when I talk with patients and my medical colleagues, the question of clinical meaningfulness immediately comes up, and I think one of the best ways to think about this is in terms of potential

time gained. And what I mean by that is the difference in the time that it takes a person, on average, in the donanemab group in this case, to reach the same level of decline as the average person treated with placebo; and when you look at this across the overall group, it was over 5 months out of 18 months. And importantly, I think when you look at the earlier pathologic group, the low-medium tau, this exceeds 7 months out of 18 months in this study.

Now, perhaps most excitingly, from my point of view, is that I think there's increasing evidence that this class of anti-amyloid antibodies is disease modifying. We are changing the underlying pathophysiology of Alzheimer's disease, and that means that we have the potential for even greater time gained over a longer time period.

Now, this is an extrapolation model because, of course, we don't yet have six-year data in this population, but these models consistently suggest that especially if we start with the very earliest population -- in this case low-medium tau, very

early symptomatic MCI -- we can see a dramatic increase in the time gained over years out from starting these medications.

Now, as you can tell, overall, I am fairly positive about the donanemab program, but I do want to address some of the novel clinical trial design elements that were employed here, and as Dr. Buracchio mentioned, the potential thorny issues and how do we translate these clinical trial elements into clinical practice, so I want to address three specific ones: first, the use of tau PET to define eligibility; second, the cessation of treatment once people became amyloid negative; and perhaps most importantly, the risk-benefit considerations related to ARIA.

So let me begin with tau PET. Now, I've been working with tau PET as an extremely valuable research tool for over a decade in research studies, and I think it's an incredible tool to be able to define the anatomic location, help us stage individuals in research studies; and of course, I was thrilled to see evidence that there were

greater treatment effect sizes at the earlier stage of pathology, as you can see here in an MMRM model across the full range of tau pathology, but I don't think that it is practical or necessary to require tau PET for use in the clinic. There's limited availability and there is no quantitative standardization available for clinical use right now for tau PET.

I'm worried that requiring this would delay starting therapy in individuals when every month may count, and importantly, I'm worried this would further limit access for underserved populations who are already getting diagnosed and started treatment too late if we put an additional requirement in place for use of this therapy.

And perhaps most importantly, although earlier does look better, I think that there is evidence that the clinical benefit was observed across the full range of tau. Even though it was more in the earlier group, it was seen even in the high tau group; and therefore, I don't think it is necessary to require tau PET, and I personally

would feel comfortable treating people in this early symptomatic range of Alzheimer's disease without knowing their tau PET value.

Now, stopping the treatment once the amyloid is removed, I have to say that variable time to cessation of treatment added a lot of complexity, I think, to understanding this trial, and I have to admit that I was very skeptical of this approach at first. Of course, this approach is used in multiple other chronic diseases, and I have to acknowledge it can decrease patient burden and it decreases cost and healthcare utilization; but really, I was convinced when I saw these data that even though half of the patients stopped by a year, there was still an increase in the widening of benefits once those individuals were stopped and were continued in a blinded fashion on placebo.

I do think there have to be ongoing studies to evaluate longer term outcomes once people are off therapies per year, and I think it is very possible that future approaches may require intermittent dosing if individuals accelerate in

their decline.

Now to amyloid reduction and ARIA, I think the totality of the data, both across the field and within anti-amyloid antibodies, suggest that aggressive amyloid reduction is necessary and that, overall, greater amyloid reduction is associated with greater clinical benefit; and on the upper right is just a review article I published with Adam Boxer last year looking at this.

Now, ARIA I believe is an on-target adverse event, meaning it is in the mechanism of action of amyloid removal, moving it from plaque into the perivascular space and out of the vascular. This is part, unfortunately, of what I think is the mechanism of at least one of the ways the brain -- we can remove amyloid.

I'm showing you here on the bottom of the slide, and I wanted to show you what ARIA looks like, and also to show you evidence that we often see ARIA occurring in a focal and temporal relationship with amyloid removal. This is back from the bapineuzumab days -- I've been working on

ARIA for a long time -- and what you can see here is in areas where there was focal amyloid removal, you can see the appearance of edema, ARIA-E, and later followed sometimes by ARIA-H in those areas. So I think, unfortunately, with our current approaches with anti-amyloid antibodies, it is unlikely that we're going to be able to completely avoid ARIA and still achieve the amyloid reduction that appears to be necessary for clinical benefit.

Now overall, I do think that ARIA is a manageable adverse event. Symptomatic ARIA is relatively uncommon and, fortunately, these serious adverse events are quite rare, but it is critically important to try to minimize the risk of ARIA with careful MRI monitoring, particularly in APOE ε4 carriers. We have to continue to inform the broader medical community about ARIA detection and management, and I don't just mean neurologists; I mean emergency room docs, stroke docs, geriatricians, PCPs, who care for patients with Alzheimer's disease and dementia who are going to encounter ARIA, and the post-approval, real-world

data will be critical to help improve our understanding, particularly of the risk for symptomatic ARIA.

Most important, we need to have detailed discussions with the patients and their care partners regarding their potential individual risk-benefit, but I think we need to allow people themselves and their loved ones to make these risk-benefit decisions for themselves with informed discussions with their care providers.

Now, I want to bring up a special population that I imagine you guys will be discussing as you think about donanemab, and that is ε4/4 homozygotes. I think the data in this program, and in all programs with anti-amyloid, plaque-reducing antibody, suggests that the risk of ARIA is higher in APOE ε4/4 homozygotes.

Overall, I think there is similar evidence of directionality of benefit. As you will notice, the confidence interval crossed zero here for the ε4/4 homozygotes, but it was a smaller group in this trial and other trials. And if there is

slightly lower benefit, I think it could also be related to that there's lower exposure overall in this group because there are greater dose suspensions due to ARIA in these trials.

APOE ε4/4 homozygotes desperately need treatment options. They've often seen Alzheimer's disease in both of their parents and they have an extremely high risk of progression to dementia. On the right, I'm showing you an article we published in Nature Medicine last month. Individuals with 2 copies of ε4 by age 65, more than three-quarters of them have a full complement of brain amyloid, and by age 65, more than half of them are already symptomatic, often with dementia by this age. So we need to be able to have something to offer these individuals, and waiting for months or years for additional studies may be too late for some of them. So personally, although I acknowledge the risk, I would consider careful dosing with monitoring in ε4/4 homozygotes.

So I am thrilled that we're in a new era of Alzheimer's disease treatments and I think we have

to take Alzheimer's disease seriously, and serious diseases require aggressive treatments. There have now been four studies that suggest that many older people fear Alzheimer's disease more than they fear cancer. We commonly in cancer allow treatments with significant debilitating side effects for a few months gained in survival, which of course is important; and historically, patients and docs have thought there's nothing we can do about Alzheimer's disease, but here we are, after a quarter of a century, when we finally have evidence that we can at least bend the curve of decline with substantial reduction of amyloid.

I think it's very valuable to have multiple treatment options for patients to consider, and even though I don't think antibodies are yet perfect, we haven't hit the full home run, and we will continue to try to maximize the clinically meaningful benefit. But right now, it is critical to do whatever we can to have an impact, to slow this terrible, inexorably progressive disease, and allow older people to be able to enjoy this time

with their families that they have worked all their lives to have. Thank you so much for your attention, I'd be happy to answer questions, and I'll turn it back to Dr. Hyman to moderate.

DR. HYMAN: Thank you, Dr. Sperling.

I'm happy to take any questions from the committee.

Clarifying Questions to the Applicant

DR. MONTINE: If I may, we will now take clarifying questions for Lilly. Please raise your hand to indicate if you have a question. When acknowledged, please 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.

Mary, please?

DR. CUDKOWICZ: Hi. Mary Cudkowicz. I'm not sure who to answer this. Talking about the tau levels, so I understand why it was used to get rid of slow progressors and to stratify; two questions, one was the relationship of blood tau levels to

PET. I get that we can't do PETS on everybody, but can we do blood levels? Would they be helpful?

The other related question was, we know from your studies that you can lower amyloid in the no-tau group. We don't have clinical efficacy; we kind of have a leap of faith that if you lower amyloid that might be -- but will you learn that in your preclinical study? Will we eventually have that type of data?

DR. HYMAN: I'm happy to take those questions. For the first question, I'm going to turn it over to Dr. Mintun to comment on the p-tau and how that correlates to amyloid tau scans. I believe that was your first.

DR. MINTUN: Mark Mintun, neuroscience. It's a really interesting area, and a lot of different reports have come out that there is an overall correlation of p-tau levels in the blood versus tau PET, the difficulty with correlations of maybe 0.7, something like that. And indeed, when you look at it as a categorical -- in other words, if you set a threshold for the p-tau, many of the

studies have shown incredibly good prediction of amyloid positivity on PET and tau positivity on PET -- once you have an amyloid positive person, there seems to be actually a big drop off of correlation of p-tau levels to tau PET. So this does not look like we can use that as a substitute.

DR. HYMAN: For the second part of your question about clinical efficacy in the no and very low tau group, TRAILBLAZER-3, which is our preclinical study specifically, that study is obviously a different population. These are patients who have pathologic evidence of disease in their brain but no reported clinical symptomatology, or minimal clinical symptomatology. Those patients are ascertained on the basis of a positive P tau blood test. We're not prospectively characterizing the tau levels in the brain by PET, so we won't be able to answer the question. It's also a clinically distinct population.

One thing I did want to bring up, though -- could I have the slide showing the efficacy of CDR sum of boxes in the low and medium

MCI population? While they're bringing that up -- here it is actually. Thank you.

Obviously, absolutely correct that we didn't enroll the no and very low tau patients in our study mainly because we just needed to have a population that could have events during an 18-month period; however, if you look within our clinical trial at the population that is most proximate to the no and very low tau -- our earliest patients, and these are patients that have mild cognitive impairment, so their earliest clinical stage, and these are patients with low or intermediate levels of tau -- indeed in that group by both IADRS and CDR sum of boxes, you see approximately 50 to 60 percent slowing.

So I think that although I can't speak to a population we didn't enroll in our clinical trial, I think these data speak to when you identify patients with the earliest pathologic disease burden and the earliest clinical symptomatology, they have the largest effect size, which is what we would expect in an irreversible cognitive disorder

like Alzheimer's. Thank you.

DR. MONTINE: Dr. Follmann, you're next.

DR. FOLLMANN: Yes. Thanks. I had a couple of questions. The first one has to do with the effect of the treatment by baseline amyloid level. I didn't think I saw that in the presentation or the materials that were sent.

DR. HYMAN: Yes. There was no differential effect by baseline amyloid level. The population that we enrolled in this clinical trial had quite high levels of amyloid, and they're at the saturation of measurement by amyloid PET scan, so we don't really see a differential effect by amyloid level. What we do see is that the patients that come with the highest amyloid level, as you would expect, take longer to clear their amyloid.

DR. FOLLMANN: Yes. I have two more questions, if I can. The second one has to do with antidrug antibodies, which you noticed in a large percentage of the patients, and also that effect with the idea of intermittent dosing coming along later possibly. So have you thought through that

or done studies about that?

DR. HYMAN: A high percentage of patients, approximately 90 percent of patients, do develop neutralizing antidrug antibodies, but at a level that does not bring the exposures below clinically relevant clearance thresholds for the compound. Is your question about whether there's unique safety considerations in the presence of them? I just want to make sure I'm answering your question accurately.

DR. FOLLMANN: Well, I think it's thinking more to the future with intermittent dosing. Maybe there would be more of an issue with prime boost de facto with the monoclonal over a year or so between intermittent doses.

DR. HYMAN: Even within our study population, we see a range of antidrug antibodies or neutralizing antidrug antibodies, and even in the patients with the very highest titers, they don't have AUC levels that drop below the relevant clearance thresholds. So we don't think that this represents a unique issue, although we have to

acknowledge, very important, that we haven't studied that prospectively, so that is an evidence gap that we'll have to generate in the postmarketing setting should the drug be approved.

DR. FOLLMANN: Then one final question has to do with CO-27, which looked at the lowering of the -- yes. This model I guess assumes the same effect, the same lowering the progression for each one of the different categories. You had four different categories of disability, and I was wondering if there was a greater treatment effect, longer delay for the earlier categories.

DR. HYMAN: Yes. I'd like to answer that in two parts. Can I have the progression-to-moderate dementia? And then I'll come back to this slide. Perfect.

In our study population of early symptomatic Alzheimer's disease patients, we wouldn't expect, during an 18 month treatment, for many patients to cross into the CDR Global Score 2 stage of dementia. This is the stage of dementia in which their Alzheimer's disease is affecting many of

their daily activities and they lose independence as a result of their Alzheimer's; but we do see some, and in that population -- or within patients to progress to the global stage 2, there's a 50 percent decrease in patients treated with donanemab.

I think the other way to look at the analysis that you just questioned is to look at it as a shift table analysis, and I just want to orient you to what we're looking at here. This is looking at the first shift of patients from their prior stage to the next global score. So if a patient moved twice, they're not represented the second time here; this is just their first shift. And again, to remind you, there are equal numbers of patients in the treatment arm, so roughly equal numbers of patients at risk, and you can see that within each CDR Global Score category, there are more patients progressing to the next stage on the placebo arm than the donanemab arm.

DR. FOLLMANN: Thank you.

DR. MONTINE: Next is Cindy.

DR. CARLSSON: Cindy Carlsson, University of Wisconsin. I have a few questions. One's fairly straightforward, but on those who had the infusion-related reactions, you said that 60 percent did not have another one when they were rechallenged. Were they premedicated with therapy?

DR. HYMAN: We've looked at this carefully. There were a variety of approaches that were taken by sites, and patients who were premedicated for the second infusion, or patients who were not, there does not appear to be a differential outcome. So we don't have data to support that a specific intervention lowers the risk of infusion-related reaction in patients that have experienced them.

DR. CARLSSON: Thank you. The other question is, if you could go to slide CO-32, with this one, just to clarify, it says at the bottom, "the donanemab completed dosing." Are those sample sizes the number of people who completed dosing at that point in time? It says "301 at baseline." If you could clarify those sample size numbers. And just to clarify, does this include all of those

randomized to donanemab with intent to treat even if they were stopped, even if the therapy was stopped and then switched to placebo?

DR. HYMAN: I think I understand the question. If I don't answer it, please just come again. This was an analysis -- I just want to start with a caveat that this was not meant to be a definitive analysis, but what we did want to do is understand what the outcome was in patients who discontinued donanemab by having achieved the amyloid clearance threshold.

So the 301 patients are the patients in the treatment arm who discontinued at 6 or 12 months during the study period, and they're compared to all patients in the placebo arm. So what we're showing here is that among the patients who discontinued at 6 or 12 months, there appears to be separation of the curve at the later timepoints in the study that's greater than earlier, again, consistent with disease modifying.

We recognize that we're comparing only the patients that achieved clearance in the donanemab

arm to the placebo arm, and we did a propensity match analysis with placebo patients as well, and the findings look very similar to this. So there really was no effect by that selection of all placebo or propensity-matched placebo patients.

DR. CARLSSON: So was this analyzed, both the CDR sum of boxes and the IADRS, or just CDR sum of boxes?

DR. HYMAN: Yes, and the results are consistent both ways. We just have generally favored presenting CDR sum of boxes data here because we expect that to be the primary basis for labeling as FDA's preferred metric.

DR. CARLSSON: Thank you.

DR. MONTINE: Tanya, you're next.

DR. SIMUNI: Tanya Simuni, a couple of clarifying questions. What was the percent of patients with no evidence of tau who were excluded from the ACI study, who would have qualified otherwise, percent absolute number versus the absolute number of individuals who were recruited with those tau characteristics into the extension

study?

DR. HYMAN: Let me bring up this slide. It's a little bit hard to answer your question completely directly because it's somewhat impacted by the order in which patients had their screening scan; so a patient that had an amyloid scan first, and then a tau scan second, or reverse, but approximately 20 to 25 percent of patients were excluded on the basis of not meeting the tau threshold, and those patients were offered enrollment in the the addendum study, as the FDA mentioned in their opening remarks, to generate pharmacodynamic measures.

Dr. Sperling has educated me that in point of fact, it's a very small percentage of Alzheimer's patients that don't have tau pathology in their brains, but obviously we had to set a threshold in this program with the tau study, and I hope that answers your question.

DR. SIMUNI: If I could extend the question, my understanding is that the number of individuals who were enrolled in ACI with those criteria was

about 250.

DR. HYMAN: That's correct.

DR. SIMUNI: How does that absolute number correspond to the number who were excluded for those criteria?

DR. HYMAN: Dr. Sims, I don't know if you could address this question. The addendum I don't believe was available the entire study duration, so I wouldn't expect it to match 1 to 1, but maybe Dr. Sims --

DR. SIMUNI: I understand.

DR. SIMS: John Sims, Head of Medical. I'm not sure I completely understand your question, but let me do a little clarification here. In the main study, you could get a tau scan or amyloid scan, whatever one was available first. The 25 percent up there that are tau negative actually is an over-estimation of tau, low to no tau. That's only about probably 8 percent. The reason is, is that people who don't have tau, many of them also have no amyloid because you have to pass through amyloid to get to the tau stage.

So if you just ask the question, how many amyloid positive people are on that low to no tau spectrum, that's approximately about 8 percent that you would anticipate; and as mentioned, the addendum came around, and you could only go into the addendum if you were amyloid positive. So there's a bunch of tau negative people who aren't amyloid positive and wouldn't be eligible for the addendum. I don't have that precise number for you, but I hope that gives some characterization.

DR. SIMUNI: No, the percentage -- thank you very much for clarification.

If I may, one very quick clarification regarding slide CO-46. Bullet point 4 of those who were rechallenged, 60 percent did not have another IRR. What percent of individuals who did develop IRR were not rechallenged?

DR. HYMAN: Dr. Melissa Veenhuizen?

DR. VEENHUIZEN: Melissa Veenhuizen, Global Patient Safety. Approximately 4 percent, 3.8 percent, discontinued and did not get a rechallenge, but they discontinued due to the

infusion-related reaction.

DR. SIMUNI: Thank you very much.

DR. MONTINE: Kathleen?

DR. POSTON: Thank you. Kathleen Poston. I wanted to draw attention a moment to the potential functional unblinding due to ARIA in the treatment group. My understanding was that a sensitivity analysis was done to take this into account, and this is because when individuals develop ARIA, they may have additional MRI scans for monitoring, and both the patient and the physicians could be alerted to the fact that something is going on and potentially be alerted to the fact that that person is in the treatment group.

Now as was mentioned, ε4/4 carriers have a higher risk of ARIA, and therefore, more of them would have had this potential functional unblinding, and I believe the numbers were 55 percent in the treatment group, and 22 percent in the placebo group of 4/4 carriers had some form of ARIA during the trial.

Just so I can understand the sensitivity

analysis, if the 4/4 carriers are more common in the treatment group and the sensitivity analysis then takes them out, that means that there would be less 4/4 carriers to be considered later on, which might unbalance the group so that there's more of the 4/4 carriers considered in the placebo group and possibly artificially show worsening in the placebo group; if that could be addressed, please.

DR. HYMAN: Absolutely. If I understand the question correctly, and please correct me if I'm wrong, I think the question is really about how functional unblinding could potentially impact the interpretation of the efficacy endpoints, and then within the APOE ε4/4 homozygote group, which has the highest rates.

DR. POSTON: Yes.

DR. HYMAN: Okay. Perfect. We recognize the potential for this, and we took several elements in the design of the clinical trial itself to protect it from functional unblinding. Importantly, the people who performed the CDR sum of boxes and IADRS rating scales were blinded to

adverse events or study conduct, so they were a separate group that were not influenced by that. We also made sure that the Lilly team themselves, the safety and efficacy teams, were divided so there wasn't any issue at the sponsor level with unblinding, and of course we prespecified several analyses as well.

I think the the way to answer the second part of your question, I believe, is that, really, the purpose of the sensitivity analysis is to ask the question, is there evidence that functional unblinding impacted the rating at the study level? And the answer is no. Obviously, within individual groups, it becomes hard then to measure the effect within those individual groups, but we don't see any evidence that there are unique issues with that group, but it's important to recognize that we can't rule out every single group.

One other thing I would mention is that while it's absolutely true that there's more ARIA obviously in the donanemab-treated group, as I think the FDA also mentioned in their briefing

document, ARIA-H is actually seen even in the placebo arm, so it's not perfect functional unblinding even if those protective measures were not put in place.

DR. POSTON: If I could have one quick follow-up, again, really diving into the the protecting of the blind, which is obviously so critical, on an individual subject level, internally, did you look at spaghetti plots to consider whether or not, after their ARIA, there were changes in their functional ratings or any of the outcomes that could have potentially affected those events that were happening, regardless of which group they were in?

Again, as you said, placebo also could have had ARIA and could have inappropriately thought that that individual was in treatment when they were not, but looking at that level to make sure that there wasn't alteration in the functional measures. Particularly, the subject reported ones like the CDR because the patient would have known that they had additional MRI scans.

DR. HYMAN: I understand. I'll have Dr. Sims address your question.

DR. SIMS: John Sims, Head of Medical. So for the APOE ε4 carriers, for the homozygotes, we have to remember there are only about 17 percent of the whole population, so actually most of the ARIA is going to be represented by the heterozygotes.

Let me pull up this slide here first. This is the centering analysis -- it's the bottom row -- preplanned just to address this idea. There's always a concern of this functional unblinding, and we have to be cognizant of it, and it's preplanned to test this way. So that bottom row is that test, and actually it's beyond that test. It includes the infusion-related reactions as well

Here, what we're doing is all your data is in the study and everything is censored after the ARIA, so any information after that is no longer included. So this will include even all the homozygous, heterozygous, or non-carriers who have an event. If you want to see that as a curve,

that's here, and this is what it looks like with all that data censored, also still maintaining quite a positive treatment effect.

DR. POSTON: So this has the individuals who had one of the treatment-related effects either in placebo or in treatment censored out --

DR. SIMS: That's right; data's out.

DR. POSTON: -- centered out.

DR. SIMS: Yes.

DR. POSTON: Do you know the percentage of ε4 carriers by week 76 that are still in the treatment group versus the placebo group? How much imbalance is it if more ε4 carriers potentially had ARIA and were taken out of the treatment group?

DR. SIMS: I don't have a number there for you. Generally, at a gestalt level, it would start to get enriched for the non-carrier since they have the lower rate.

DR. POSTON: Yes.

DR. HYMAN: I understand the question. Let's see if we can get those data for you and bring it back after the break before the

committee's discussion section.

DR. POSTON: That would be great. Thank you.

DR. HYMAN: I understand the data. I don't think we have it at our fingertips. I apologize.

DR. MONTINE: Nilufer?

DR. ERTEKIN-TANER: Nilufer Ertekin-Taner, Mayo Clinic. I have a few questions. The first has to do with ε4 carriers and adverse events partitioned by race and ethnicity. The premise of the question is that African Americans and Latino Americans are at higher risk of Alzheimer's disease, but the risk of ε4 in those populations are different than non-Hispanic whites, specifically less, and yet African Americans, for example, may have more vascular burden.

So in light of that, have you looked at the adverse events in ε4 separated also by race and ethnicity?

DR. HYMAN: I'm not sure.

Dr. Veenhuizen, have we done that?

DR. VEENHUIZEN: We have no [inaudible -

2:16:49].

DR. HYMAN: That could be something else we can try to work on during the break. I will just say, although we obviously did not enroll enough of those populations, we don't see clear evidence of safety differences by race or ethnicity, but I understand the question you're asking. We'll see if we can generate that table for you.

DR. ERTEKIN-TANER: Then the other question has to do with follow-up on thrombolytic-related worsening. I realize the numbers may be low, but with that being said, do you have data on thrombolytic treatment after you stop the treatment with donanemab?

DR. HYMAN: Dr. Melissa Veenhuizen?

DR. VEENHUIZEN: Melissa Veenhuizen, Global Patient Safety. Are you talking about specific cases where there may be an event after they've stopped donanemab treatment in the use of a thrombolytic?

DR. ERTEKIN-TANER: In the overall population that you followed after stopping the

treatment, do you have data on how many were treated with thrombolytics and what was the outcome?

DR. VEENHUIZEN: Yes. So what I can show you is during treatment where we had 10 percent of the donanemab patients that used an anticoagulant and 40 percent used an antiplatelet. This is in the donanemab placebo-controlled time period, and this represents the frequency of ARIA-H on the left-hand side and ARIA-E on the right-hand side, based upon whether no antithrombotic was used in that light gray bar at 30 percent and 25 percent -- and then whether at least one antithrombotic; aspirin; non-aspirin platelet; or even dual antiplatelet therapy; or just the use of an anticoagulant was used -- and shows the frequency of ARIA-E and ARIA-H. We did not have ARIA-E or H occurring with the use of thrombolytics during the placebo-controlled time period.

DR. ERTEKIN-TANER: But to be clear, this is during the --

DR. VEENHUIZEN: It is during treatment. We

do not have that after treatment.

DR. ERTEKIN-TANER: Okay.

And one last question pertinent to anaphylaxis, again, this was very small, but what was done afterwards?

DR. VEENHUIZEN: As far as treatment, for the anaphylaxis treatment --

DR. ERTEKIN-TANER: Treatment and follow-up.

DR. VEENHUIZEN: -- they were followed until the actual event resolved. Even in those that had a reported anaphylaxis, the majority of those resolved, if not on the day of infusion, by the next day, so various consequences or outcomes.

DR. ERTEKIN-TANER: Treatment was resumed.

DR. VEENHUIZEN: No. In those that had a serious adverse event like anaphylaxis, they did generally discontinue treatment.

DR. MONTINE: Daniel?

DR. PRESS: Dan Press. I have a quick question and a longer question. The quick one is, of the 3 deaths from ARIA in the trial and the two open-label extension deaths, do you know how many

of them were APOE ε4 homozygous?

DR. HYMAN: Yes, we have looked at it carefully. We have a table to show you.

Dr. Melissa Veenhuizen, maybe you can come up and narrate this.

DR. VEENHUIZEN: Yes. We have a summary of the information on the population, but none of these were homozygotes, APOE ε4 homozygotes, with the fatal event. You can see here in the relevant information in the right-hand column, we had a non-carrier, a heterozygote in actually another four cases, no homozygotes.

DR. PRESS: Thank you.

My second question is a little bit trickier. The argument has been made that high tau would be hard to recognize in the clinic because of the unavailability of tau scans, but patients with high tau also are more cognitively advanced as a general rule. Have you looked at whether there's a cognitive profile that could act, in essence, to pick out the group that would have fit into the high tau group with relatively good sensitivity and

specificity, for instance, if the MMSE was below 22 or something like that?

DR. HYMAN: Yes, we've looked at this.

Dr. Mintun, do you want to address that question?

DR. MINTUN: Mark Mintun, neuroscience. We did look at that. That's fascinating. While you do this by groups, and it's clear the more impaired have more high tau, the more high tau have more impaired, it is actually quite poor in being able to predict high tau. The logical explanation that we could find is that too many people have other comorbidities. Small, little, other vascular changes can cause more cognition changes in the absence and, in fact, there are some extreme situations of people with quite high MMSEs, mild cognitive impairments, that ended up with very high tau and very rapid decline. So it is very, very hard to predict the tau from the cognition, and we gave up.

DR. MONTINE: Merit, you're next.

DR. CUDKOWICZ: Merit Cudkowicz, Mass

General. I wanted a little more information about how maybe physicians would be making decisions about stopping the drug for the amyloid. In particular, do you have any data on why some people clear it faster, as well as if people accumulate faster; and what would be a proposal for how the physicians would determine when to stop the drug and maybe when to consider restarting it?.

DR. HYMAN: Absolutely. We recognize that this was a different feature in our clinical trial design. We really do look forward to hearing the committee's viewpoints on this; it's an important topic, and we implemented it, really, for two primary reasons. One is, scientifically, we didn't see clear justification for continuing our medicine when the target of the medicine was not detectable in the patient's brain anymore, and we really did want and listened to the community about the overall burden that these therapies represent, and looked to minimize that. So, really, duration of therapy I think is an unanswered question for the entire class of medicines.

To answer your question, I think you had two specific questions. One was about what are the predictors of clearance, and really, the singular predictor of clearance is the burden of amyloid that the patient comes to the study with. The rate of actual removal is fairly consistent, so patients that have higher levels coming in take longer to clear and patients with lower levels clear faster. It should be said that nearly everybody treated with this medicine has dramatic lowering, and although not every patient met criteria for stopping at the end of treatment, we're obviously continuing to follow patients that were crossed over to the open-label extension to follow the kinetics of their amyloid decrease.

But really, the second part of your question, if I understood it correctly, is really about, okay, you did this in a clinical trial, but how are you going to educate providers, and how is this actually going to be implemented in clinical practice? So maybe I can make a couple of comments about that.

Number one, every patient and provider may decide this is not right for them. We acknowledge that. I think it's worth saying that. When we look at what could be a reasonable timepoint to repeat an amyloid PET scan to determine clearance, about one year seems like a pretty good timepoint to do that. We predict that at one year, approximately two-thirds of patients would have a visually negative PET scan and be able to discontinue, should they want to do that.

Obviously, exactly what you're optimizing for, if you're a healthcare system looking to absolutely minimize the use of the product, you might bring that a little bit earlier or a little bit later, but I think, in general, about one year we believe represents the sort of optimal timepoint for most patients.

DR. MONTINE: Sarah?

MS. DOLAN: Sarah Dolan, consumer representative. My question is around slide 44. When we were presented that slide -- it's regarding mortality -- there were 3 deaths due to ARIA, and

then you added another MRI, and two of the deaths would have been caught had the MRI been added to the study before that; is that correct?

DR. HYMAN: I wouldn't go as far as to say that. I want to be very clear about the limitations of our data. I think that's really important, to recognize that we think there are measures that we can put in place, including additional MRI scans, to minimize or reduce the chance of symptomatic or serious ARIA, and even the most severe consequence, death. But I don't want to represent here that we can entirely eliminate that risk. I don't think that's fair, and I don't think we have data to support that.

So I want to clarify the point we were making here --

MS. DOLAN: Okay.

DR. HYMAN: -- which is that what we saw -- and again, this is not a preplanned analysis; we're just telling you the data that we have across our program -- is that when the MRI was added prior to the second infusion, we saw lower

rates subsequently of serious ARIA or symptomatic ARIA. Why do we think that's happening? Because we are identifying the patients who clear amyloid the most rapidly, have asymptomatic ARIA on their scan, and then by intervening typically by holding therapy and allowing that to resolve, we actually increase the total rate of ARIA but decrease the rate of symptomatic ARIA, which is the goal.

So I hope I've clarified what we were trying to communicate about this.

MS. DOLAN: I'd love to hear what what Dr. V was saying when she made this point on slide 44.

DR. HYMAN: You mean the exact words she was saying?

MS. DOLAN: Well, yes.

DR. HYMAN: Dr. Veenhuizen, can you come up and address it?

DR. VEENHUIZEN: Melissa Veenhuizen, Global Patient Safety. So what we were trying to communicate is that we have added these additional MRIs to aid in the detection earlier before these events may become serious or symptomatic, so that's

why we've recommended additional MRIs in the proposed labeling beyond the clinical study.

MS. DOLAN: Okay. Thank you very much.

DR. MONTINE: Nilufur?

DR. ERTEKIN-TANER: Nilufer Ertekin-Taner. You mentioned -- it may not have been you personally, but it was mentioned during the presentation that you included more patients with higher risk, including superficial siderosis, and of course, cerebral amyloid angiopathy and superficial siderosis can go hand in hand, and ε4 is a risk factor for them both.

Have you done analysis to look at the risk of side effects, especially ARIA-H vis a vis pretreatment CAA and superficial siderosis? That's question number 1.

DR. HYMAN: Yes. Let me see if we have that here, and maybe Dr. Veenhuizen, can you come up and address this slide?

DR. VEENHUIZEN: Yes. So for the specific on baseline microhemorrhage and superficial siderosis, we have seen they are somewhat

predictive. In this particular case, this is illustrating frequency of ARIA-E. So you can see that the frequency of those on the donanemab arm, shown in the darker blue, if they had zero superficial siderosis, it was about 23 percent; if they had the presence of one lesion of superficial siderosis, or one area, that ARIA frequency went up to about 50 percent. On the right-hand figure, you can actually see also microhemorrhages, whether it's 0, 1, or 2 in this particular illustration, and again, the frequency increases for ARIA based upon the frequency or the number of the microhemorrhages present.

I think this additional slide may be helpful to characterize the fact that we analyze the risk factors from the All Dona population, and we saw that ARIA-E risk was consistently driven by the APOE ε4 genotype, and was the highest risk for the homozygotes. Then the number of baseline microhemorrhages, the higher number, the more risk you would have for ARIA, the presence or absence of superficial siderosis, with the presence increasing

risk, and then the amount of baseline amyloid, although that was a very small contributor relative to these other three risk factors. Additionally, you can see below that band a number of risk factors that were also evaluated, and we did not see a consistent impact on the frequency of ARIA.

DR. ERTEKIN-TANER: Thank you.

The second question is related to clinical use. For physicians, it will be extremely useful to have categorization of risk according to the different risk factors. What are your plans of providing that concrete risk information, based on the different types of risks that an individual patient would have?

DR. HYMAN: Absolutely. We completely agree that we have to educate the provider community extensively on this topic that this is the primary risk of these medicines. We plan to do that in a variety of ways. We published extensively these data at various meetings and journals, so in the scientific literature, that's one, but obviously we're here to discuss many other channels as well.

Through our labeling, we have patient information cards that we will give patients to carry with them, so if they present with these symptoms, providers that are unfamiliar with these symptoms, they have that information handy. We have multiple education initiatives. We know our colleagues that are commercializing other medicines are doing the same.

I also know that the FDA in their presentation later today will have some specific guidance about how they plan to educate first-line providers to recognize ARIA in patients presenting with stroke-like symptoms. So this is going to be a concerted multi-year effort to educate providers about the risks of ARIA and make individualized treatment decisions for their patients.

DR. ERTEKIN-TANER: Thank you.

Then I have a question pertinent to CO-28, which looks at the efficacy divided by ages, and obviously age is less than 65. The numbers are small, but also patients with ε4 homozygosity tend to have younger ages. So my question is, have you

looked at the ε4 homozygosity and the adverse effects in that youngest age group? I wonder if the lack of efficacy is just the numbers or whether the treatment had to be stopped because of adverse effects.

DR. HYMAN: We have, and actually it's not APOE enrichment in that subgroup that's driving that, and in fact, when you look on a more continuous function by age, you don't see this trend. It's the effect of a small subgroup and the specific cutoff applied.

DR. MONTINE: Thank you everyone. If I may, we're done. We're going to take just under a 15-minute break, so I'd ask if we could please return to start at 11:15. Thank you.

(Whereupon, at 11:02 a.m., a recess was taken, and meeting resumed at 11:15 a.m.)

DR. MONTINE: Welcome back. We'll now proceed with the FDA's presentation, starting with Dr. Kevin Krudys.

FDA Presentation - Kevin Krudys

DR. KRUDYS: Thank you.

Hi. I'm Kevin Krudys. I'm going to provide a clinical overview of the evidence provided to support the effectiveness of the drug for the treatment of Alzheimer's disease. Donanemab is a monoclonal antibody targeting brain plaques. The proposed indication is for the treatment of early symptomatic Alzheimer's disease, specifically patients with mild cognitive impairment or mild dementia stage of disease. There are two notable clinical design features of the program, which will be highlighted in the presentation and can motivate some of our discussion today.

First, the applicant met the tau level that's measured by PET imaging as an enrichment strategy in their studies. As such, patients with no or very low tau levels on PET were excluded from the efficacy studies. Second, the applicant did allow for a stopping of dosing based on reduction of amyloid PET.

The clinical studies that are relevant to the evaluation of efficacy are listed in the table on this slide. Study AACG was a relatively smaller

placebo-controlled phase 2 study. This presentation will focus mostly on the results of Study AACI, the large placebo-controlled safety and efficacy study. We also considered the data from the single-arm safety addendum, the Study AACI, in which, open label, a study drug was administered to approximately 1,000 subjects. Studies enrolled a similar population of patients with early AD.

The key endpoints were similar in studies AACG and CI and included assessments of cognition, function, and biomarkers. The safety addendum did not include assessment for clinical endpoints, but it was the only study that included patients with no or very low tau levels. The phase 2 study included the enriched population of low-medium tau, and the phase 3 study expanded on that population to include patients with high tau levels. Dose cessation based on amyloid PET levels was allowed in all studies.

The primary endpoint for studies AACG and AACI is the Integrated Disease Rating Scale. The scale is a combination of two other clinical

assessments, the ADAS-Cog 13, a cognitive assessment consisting of clinical ratings, and the ADCS-iADL, which is a rater administered questionnaire for informants that assess activities of daily life.

Twice, the division expressed its concerns to the applicant with the choice of the primary endpoint, that effects on the intervention may not be considered clinically meaningful or can reflect the effects on the two components of the scale. The division advised the applicant to retain the CDR-SB as a primary endpoint or to establish a co-primary endpoint approach for the two components of the primary endpoint, and both of those approaches are considered acceptable to establish the effect of the drug in this population.

The study screened 8,000 subjects to enroll 1,736 subjects in a 1 to 1 between placebo and treatment arm. Subjects treated with donanemab were more likely to discontinue treatment and to discontinue the study compared to subjects in the placebo arm. A total of 137 subjects were not

included in the primary efficacy analysis for the primary endpoint because they did not have a baseline assessment and any post-baseline assessment.

Key baseline characteristics were reasonably balanced between the two arms and generally represent the patient population of a stage 3 or 4 disease. Sixty-eight percent of subjects that enrolled in a population had a low-to-medium tau and 32 percent had high tau. The applicant prespecified a low-medium tau population and the full population for efficacy analysis. For presentation of the results, I will focus on the entire population because it's more relevant to the intended population.

Study AACI met its primary endpoint, demonstrating a significant reduction, a primary endpoint of 2.9 points or a 22 percent slowing at 76 weeks in the overall population. Importantly, statistically significant effects were observed for both components of the primary endpoint. The statistically significant effects were also seen

for CDR-SB with a reduction of 0.7 points in the overall population, which corresponds to a 29 percent reduction at 76 weeks.

So in this case, the consistent findings that we're seeing across the secondary endpoints, which assess distinct components of cognition and function, do help to mitigate the concerns we expressed about the choice of the primary endpoint. Statistically significant results were also observed in the low-medium tau population, a finding which I will talk about in subsequent slides, and a large reduction in brain amyloid was also observed in this study.

This slide here shows the top-line results for the phase 2 study, study AACG, conducted in patients with low-medium tau. The primary endpoint was a change from baseline for the IADRS at week 76 and demonstrated a statistically significant effect compared to placebo. The trial may not have been powered to demonstrate significant treatment effects in all secondary endpoints, but the estimates are generally consistent with those

observed in the low-medium tau population of Study AACI. The reduction in brain amyloid was also consistent across the two trials, and these results provide support for the effect of the drug.

In summary, Study AACI was a large multicenter trial that met its primary endpoint and key secondary endpoints. The treatment effect with Study AACI is supported by consistently favorable results for the primary and secondary endpoints across prespecified subgroups of interest, and the results of the smaller phase 2 study, AACG, support the effectiveness on the clinical outcomes that were observed in Study AACI.

A tau burden as measured by PET imaging was used for the enrichment in the study program. Although tau burden exists on a continuum, the applicant defined three groups for the purposes of patient enrollment and defining populations. Groups were defined both by the visual assessments and by quantitation of PET scans with standard uptake value ratios.

The applicant excluded subjects with no or

very low tau from the placebo-controlled studies because the expectation was that this population is less likely to progress during the 76 weeks of the study, but these patients are still thought to potentially benefit from therapy; but due to the slower rate of progression, the time needed to manifest the treatment effect could be longer than that of the trial duration.

Subjects who had no or very low tau were included only in a safety addendum to Study AACI. On the other end of the spectrum, for high tau burden, these patients could be less likely to respond to anti-amyloid therapy because it's possible that downstream pathological processes could dominate at this stage, and these subjects may be more likely to progress in the course of the study.

In the middle, subjects in the low-to-medium tau were expected to be likely to both progress during the study and to respond to treatments. For this reason, subjects with low-medium tau were included in both the phase 2 and phase 3 study and

were prioritized for the analysis of Study AACI. Because patients with no tau were excluded from the double-blind studies, we considered whether it's appropriate to support treatment in the entire population.

Here, we show the subgroup findings for the primary endpoint in CDR-SB in Study AACI by prespecified tau groupings, including tau terciles based on quantitative assessment and categories as defined in the previous slide. The points in the plots reflect the adjusted mean difference for the subgroups, and it is also important to consider the calculation of percent slowing, shown on the right, which takes into account the placebo decline in that subgroup.

Two important findings are, one, that a treatment effect was observed across the range of tau included in Study AACI, including patients at the higher range of tau; and the second important finding is a larger effect of treatment as expressed as percent slowing in patients in the low-to-medium tau group compared to the high tau

group, consistent with prior expectations.

To address the potential effect of the drug in a no to very low tau population, we considered data from this population enrolled in the safety addendum. Clinical outcomes were not assessed, so we stored change from biomarkers. This plot here shows the change from baseline in amyloid PET, a biomarker considered reasonably likely to predict a clinical benefit. We can see that, at baseline, amyloid burden in the no or very low tau population is lower than the population enrolled in Study AACI, but change from baseline is generally consistent with that observed in subjects with low-to-medium or high tau. This suggests that the underlying pharmacological effect is preserved across the spectrum of tau burden.

Here, we show the results for two other plasma biomarkers, plasma p-tau 217 and plasma GFAP. Both of these markers have a similar effect. We see here that the starting value is lower than in patients that were enrolled in the phase 3 study but that the trends are consistent

with what was observed in patients at higher tau burdens. It's also important to keep in mind that most symptomatic patients do have some degree of tau pathology and that the course of disease is progressive for all levels of tau. Furthermore, the pharmacologic effect on brain amyloid is anticipated to be the same across tau levels, and this has been established in subjects enrolled in the safety addendum.

Finally, the results of Study AACI suggests that treatment effect was observed across the range of tau levels and a larger treatment effect expressed as percent slowing was observed in patients with a lower tau burden.

Participants in Study AACI had a titration regimen of 700 milligrams every 4 weeks for the first 3 doses, and then 1400 milligrams every 4 weeks until study completion. Double-blind stopping of dose was guided by amyloid PET levels at weeks 24, 52, and 76. Participants treated could switch to placebo if their amyloid levels were less than 11 on a single visit or 11 to 25 on

two consecutive visits. At weeks 24, 52, and 76, the proportion of participants in the treatment arm who met the stopping criteria was 17 percent, 42 percent, and 60 percent. Twenty-nine percent of subjects who entered the long-term extension period still received the full dose of 1400 milligrams. When using data from patients who completed treatment, PET levels began to increase with the mean rate of 2.8 centiloids per year, and this rate is similar to rates observed in other clinical trials.

Although a cessation of dosing could be a reasonable approach, there are still significant uncertainties about its implementation and clinical benefit. First, the relatively short time spent in the study for patients who switched to placebo during the phase 3 study could limit the ability to assess the long-term consequences of dose cessation. Furthermore, there's not an appropriate comparative group to assess efficacy, as there was no arm in the study that included continuous dosing.

A comparison of clinical outcomes in subjects who had a cessation to the overall population is also not appropriate because patient characteristics are no longer the same in the two groups. There's also considerable uncertainty regarding the appropriate threshold for dose cessation, and although the reaccumulation of plaque is relatively slow at the mean level, the potential to restart treatment based on backload is still untested.

In conclusion, Studies AACI and AACG provide evidence for the effectiveness of the drug. Based on the understanding of disease progression, as well as results of clinical outcomes in Study AACI and biomarker evidence from the safety addendum, we think it appears acceptable to generalize the efficacy across the spectrum of tau, and specifically in patients with no or very low tau burden. And finally, although cessation of dose may be a reasonable strategy, significant uncertainty still remains.

Now I'll turn over the presentation to

Dr. Branagan.

FDA Presentation - Natalie Branagan

DR. BRANAGAN: Hello. I'm Dr. Natalie Branagan, the clinical safety reviewer for this application, and I will be providing an overview of the safety findings of donanemab. The primary source of data for the assessment of safety in this submission is the 76-week randomized, placebo-controlled period of Study AACI.

Across the development program, 2,885 patients with Alzheimer's disease have been exposed to at least one dose of donanemab given intravenously, including 853 patients exposed to donanemab in the placebo-controlled period of AACI. At the time of the 90-day safety update of the resubmission, 1,912 patients from the all donanemab pool were exposed to donanemab for 6 months, 1,057 patients were exposed for 12 months, and 432 patients were exposed for at least 18 months at the proposed dose.

This slide shows mortality observed in the placebo-controlled period of Study AACI. The

mortality assessment in Study AACI is based on an on-study approach and includes all deaths reported by week 76 regardless of whether the patient discontinued from the study. At 76 weeks, the incidence of death for donanemab is 2.2 percent versus 1.2 percent for placebo, with an estimated risk difference of 1.0 percent and a 95 percent confidence interval of minus 0.3 percent to 2.3 percent, as shown in the table.

Taking into consideration 3 amyloid-related imaging abnormally-related deaths, or ARIA-related deaths, which occurred in donanemab-treated patients, the non-ARIA-related incidence of death was 1.8 percent in the donanemab arm compared to 1.2 percent for placebo, with an estimated risk difference of 0.6 percent and a 95 percent confidence interval of minus 0.6 percent to 1.8 percent.

In the placebo-controlled period of AACI, approximately 26 percent of donanemab-treated patients withdrew from the study compared to 20 percent on placebo. After withdrawing from the

study, vital status at week 76 was not captured for these patients by the applicant. The lack of vital status information collected during the conduct of Study AACI adds uncertainty to the mortality analysis results shown in the table for which there was an imbalance in deaths observed with donanemab relative to placebo.

This slide shows time to study discontinuation observed in Study AACI. At 8 weeks, patients on donanemab started to discontinue at a higher rate than patients on placebo. This table shows causes of death in the placebo-controlled period of Study AACI at the time of the 90-day safety update. There were 3 ARIA-related deaths in the donanemab arm, considered to be related to donanemab, compared to no ARIA-related deaths on placebo. One of the ARIA-related deaths occurred in a patient who died from intracerebral hemorrhage in the setting of ARIA-E and ARIA-H. In the all donanemab pool, there was one additional death from ARIA and one additional death from intracerebral hemorrhage in

the setting of ARIA-E.

Both of the deaths from intracerebral hemorrhage were in patients with MRI findings consistent with cerebral amyloid angiopathy, or CAA, which is a known risk factor for intracerebral hemorrhage. In one case, the patient had symptoms mimicking stroke and was administered thrombolytic therapy. ARIA and intracerebral hemorrhage will be discussed in more detail later. Other than ARIA-related deaths, the remaining deaths did not appear to be causally related to donanemab and there was no unusual clustering of deaths that would suggest a causal relationship.

With high rates of missing vital status data at week 76 and its potential impact on the assessment of mortality, the agency requested that the applicant retrieve additional mortality information among patients who discontinued Study AACI prior to week 76 and for whom the vital status was not available at the time of the 90-day safety update.

Among 352 patients whose vital status was

unknown at the time of the 90-day safety update, the vital status of 52 percent was retrieved. Among the patients with retrieved vital status information, 2 patients randomized to donanemab died within 76 weeks of randomization and 6 patients randomized to placebo died. This is a correction to the slide which notes five additional deaths on placebo. Information on cause of death in these patients is not available.

Incorporating these retrieved deaths into the deaths observed during the trial resulted in 19 deaths on donanemab and 16 deaths on placebo. Limitations of these data include that the additional death information was obtained through a different approach from the approach planned in Study AACI. It was obtained from publicly available information in records, databases, social media, and traditional media. In addition, approximately 10 percent of patients still had missing vital status information and the retrieved vital status information lacked information on the cause of death.

Analyses of serious adverse events and treatment-emergent adverse events are based on an on-treatment approach, and adverse events were included for analysis if they occurred while the patient was on treatment or within 57 days of the last dose of study drug, where 57 days was considered to represent approximately 5 times the half-life of donanemab.

This table shows the most frequent treatment-emergent serious adverse events in Study AACI. Incidences presented are crude percentages. The incidence of serious adverse events in Study AACI was 16.4 percent in the donanemab arm compared to 14.2 percent on placebo. In Study AACI, treatment-emergent adverse events occurred in 89 percent of donanemab-treated patients compared to 82 percent on placebo.

This table shows the most common treatment-emergent adverse events reported in Study AACI, including ARIA-H microhemorrhage; ARIA-E; ARIA-H superficial siderosis; headache; and infusion-related reaction. These

treatment-emergent adverse events do not include individual adverse events associated with events of ARIA. Other events that occurred with higher incidence in the donanemab arm compared to placebo included hypersensitivity events occurring in approximately 3 percent of donanemab-treated patients compared to 0.7 percent of placebo-treated patients, and included events of anaphylaxis and angioedema.

Monoclonal antibodies directed against aggregated forms of beta amyloid can cause amyloid-related imaging abnormalities, or ARIA, observed on brain MRI. It is hypothesized that anti-beta amyloid antibodies accelerate breakdown and clearance of beta amyloid, which may disrupt vascular integrity and result in leakage into surrounding tissues with parenchymal or sulcal changes observed on MRI. ARIA with edema, ARIA-E, can be observed on MRI as brain edema or sulcal effusions, and ARIA with hemosiderin deposition, or ARIA-H, can be observed on MRI as microhemorrhage and superficial siderosis.

ARIA can occur spontaneously in patients with Alzheimer's disease or in patients with cerebral amyloid angiopathy. ARIA-E and ARIA-H can occur together. ARIA usually occurs early in treatment and is usually asymptomatic, although serious and life-threatening events, including seizure and status epilepticus, can infrequently occur. When present, reported symptoms associated with ARIA may include, but are not limited to, headache; confusion; visual changes; dizziness; nausea; gait difficulty; and focal neurologic deficits. Symptoms associated with ARIA usually resolve over time. The risk of ARIA, including symptomatic and serious ARIA, is increased in apolipoprotein ε4 or APOE ε4 homozygotes.

The incidences of ARIA in this presentation are based on analysis of data based on MRI data. In Study AACI, ARIA-E was reported in 24 percent of donanemab-treated patients compared to 2 percent on placebo. Symptomatic ARIA-E was reported in 6 percent of donanemab-treated patients compared to none on placebo. ARIA-H microhemorrhage was

reported in approximately 25 percent of donanemab-treated patients compared to approximately 11 percent on placebo. ARIA-H superficial siderosis was reported in 15 percent of donanemab-treated patients compared to 3 percent on placebo.

Intracerebral hemorrhage greater than 1 centimeter was reported in approximately 0.5 percent of donanemab-treated patients compared to approximately 0.2 percent on placebo. In the donanemab arm, among the 4 patients with intracerebral hemorrhage, all had risk factors for intracerebral hemorrhage, including the presence of an APOE ε4 allele in three of the four patients and findings consistent with cerebral amyloid angiopathy in two of the four patients, characterized by presence of superficial siderosis prior to the events of intracerebral hemorrhage.

APOE ε4 homozygotes have been previously shown to have an increased incidence of ARIA compared to heterozygotes and non-carriers in patients taking monoclonal antibodies directed

against aggregated forms of beta amyloid. In Study AACI, donanemab-treated homozygote APOE ε4 carriers had higher incidences of ARIA, ARIA-E, and ARIA-H compared to heterozygotes and non-carriers. The number of participants with intracerebral hemorrhage greater than 1 centimeter in Study AACI was low, and a conclusion regarding the role of APOE ε4 status on intracerebral hemorrhage greater than 1 centimeter could not be drawn.

Patients were excluded from enrollment in Study AACI for findings on neuroimaging on screening that indicate an increased risk for intracerebral hemorrhage, including any macrohemorrhage; more than 4 cerebral microhemorrhages; more than one area of superficial siderosis; presence of ARIA-E; or severe white matter disease.

In Study AACI, antithrombotic use was allowed and included the use of aspirin, other antiplatelets, or anticoagulants. The majority of exposures to antithrombotics in the donanemab arm of Study AACI were to either aspirin and

antiplatelet or aspirin in combination with an antiplatelet. A similar incidence of ARIA-H was observed in donanemab-treated patients on antithrombotics within 30 days prior to an event of ARIA-H compared to donanemab-treated patients not on antithrombotics, with an incidence of ARIA-H of 30 percent on antithrombotics compared to an incidence of ARIA-H of 29 percent not on antithrombotics.

A slightly higher incidence of intracerebral hemorrhage greater than 1 centimeter was observed among donanemab-treated patients on antithrombotics compared to those not on antithrombotics, with an incidence of 0.6 percent on antithrombotic use compared to 0.4 percent without antithrombotic use. The small numbers of intracerebral hemorrhages and small numbers exposed to antithrombotics -- other than aspirin 81 milligrams or less daily, as well as presence of other risk factors for intracerebral hemorrhage, including the presence of the APOE ε4 allele, presence of superficial siderosis and microhemorrhages, and possible cerebral amyloid

angiopathy -- limit interpretation of these results regarding the risk of intracerebral hemorrhage in patients exposed to donanemab.

In the all donanemab pool, one patient developed intracerebral hemorrhage with fatal outcome in the setting of thrombolytic use and was administered for symptoms mimicking stroke, where evidence of ischemic changes was not seen on imaging. In this case, a 70-year-old patient with medical history of Alzheimer's disease and dyspepsia, APOE ε3/ε4 carrier, and with a screening MRI that showed focal lesions of white matter disease, developed headache and slurred speech, and was hospitalized for ischemic stroke 7 days after the 5th dose of donanemab.

A CT angiogram of the head and neck vessels did not show significant stenosis, dissection, aneurysm, or large vessel occlusion. A CT of the head and brain without contrast did not identify an acute intracranial process, and CT brain perfusion showed no asymmetric, fixed, or reversible ischemic defects. Tenecteplase was administered, altered

mental status developed 1 hour later, and a repeat CT scan showed multiple hemorrhages in the bilateral hemispheres.

An MRI performed after tenecteplase administration showed the presence of severe ARIA-E in the left parietal lobe and bilateral frontal and occipital lobes; superficial siderosis in the left parietal, occipital, and temporal lobes; macrohemorrhage in the left temporal, left occipital, left parietal, and right frontal lobes; and bilateral intraventricular hemorrhages. Four days later, the patient died due to bilateral intraparenchymal hemorrhage and acute hypoxic respiratory failure.

Should donanemab be approved, the division is considering the following recommendations for labeling. Healthcare providers should be aware that ARIA can present with focal neurologic symptoms that can mimic stroke. Consideration should be given as to whether focal neurologic deficits could be due to ARIA before giving thrombolytic therapy in a patient treated with

donanemab.

Patients who develop symptoms concerning for stroke may require a more extensive evaluation and MRI to assess the etiology of the symptoms. Patients should carry a medical information card indicating that they are being treated with donanemab. Healthcare providers should carefully consider the potential benefits and risks when considering the use of a thrombolytic agent in a donanemab-treated patient with symptoms of stroke. Even though this case was observed with donanemab, we believe this can be observed with any drug that causes ARIA, and we are considering that as part of class labeling for ARIA.

Cerebral amyloid angiopathy, also known as CAA, is characterized by amyloid beta peptide deposits in cerebral blood vessels that lead to weakening of the vasculature. CAA is an important cause of intracerebral hemorrhage in older adults. Up to 90 percent of patients with Alzheimer's disease are reported to have some degree of underlying CAA with the risk of severe CAA highest

in APOE ε4 homozygotes. Findings suggestive of CAA include prior intracerebral hemorrhage greater than 1 centimeter; more than 4 microhemorrhages; more than one area of superficial siderosis; vasogenic edema; or severe white matter disease. The risk of donanemab use in patients with CAA is not well characterized.

In conclusion, amyloid-related imaging abnormalities, intracerebral hemorrhage, infusion-related reaction, and other hypersensitivity events, including anaphylaxis, are the main safety signals associated with use of donanemab. These safety findings are generally consistent with findings associated with the class of monoclonal antibodies directed against aggregated forms of beta amyloid. An imbalance in mortality was observed in Study AACI that included fatalities related to ARIA and to intracerebral hemorrhage. There is no known mechanism regarding causality for other deaths observed.

The risk of ARIA is higher in APOE ε4 homozygotes compared to heterozygotes and

non-carriers. The risk of ARIA and intracerebral hemorrhage in the presence of CAA or with antithrombotic use is not well characterized. Symptoms of ARIA may mimic ischemic stroke and the benefit-risk discussion needs to consider these uncertainties with the potential risks of use with antithrombotic or thrombolytic therapy. These risks and uncertainties can be described in prescribing information.

Prescriber and patient education regarding ARIA and surveillance for new or worsening neurological symptoms and follow-up with unscheduled MRIs, particularly in APOE ε4 homozygotes or patients with other risk factors, may mitigate some risks of ARIA associated with donanemab. This concludes my presentation, and I will now turn it over for clarifying questions to the FDA. Thank you.

Clarifying Questions to FDA

DR. MONTINE: We will now take clarifying questions for the FDA presenters. As before, please raise your hand to indicate that you have a

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 to have a specific slide to be displayed, please let us know the slide number, if possible.

Dr. Follmann?

DR. FOLLMANN: Yes. Dean Follmann, NIAID. I have a question for the first speaker. It has to do with slide 11, which shows the treatment effect by different subgroups. To my eye, it looks like there's less of a treatment effect, and look at the top slide there, and if you look at tau tercile, you see the least effect in tercile 1, the greatest effect in tercile 2, and then the third in tercile 3.

This was expected, I suppose, based on the documents I read, which thought the people who had low tau might take longer to achieve a benefit, so in my eye, we see that there, and what we don't see is tercile 0, which would be people with no or low tau, so we don't know what the treatment effect

would be there, but it might continue to diminish; I don't know.

Yet, the FDA concludes that there should be benefit irrespective of tau level, so I'm wondering where that comes from. Is it you think there should be basically no harm at the very lowest tau level or some modest benefit? Anyway, some more discussion about that conclusion.

DR. KRUDYS: Kevin Krudys here. I think we're saying we don't know exactly what the treatment effect will be in those patients that don't have tau, so a projection of what it might be. We don't know the magnitude, so we looked at the biomarkers, as I presented in the safety addendum, and I think the markers are going in the right direction, so we think there probably should be some benefit but it's hard to say how much.

To point out as well, in terms of when you're looking at point estimates and percent slowing, you have to consider how long a trial is. So it's possible that patients who were very early might show a smaller percent slowing, but if you

had waited for 4 years or 5 years, that could increase to be a higher percent slowing.

DR. FOLLMANN: I have another question, and this has to do with the population to which we generalize the study. Usually in trials, we generalize the results to the people that were in the study that satisfied the inclusion criteria, but I'm understanding that an issue here is whether we should ignore the tau level and/or -- the amyloid pathology is measured by centiloids, or whatever you call it.

So am I understanding that right; that the plan would be not to use any PET measurements at all when you try and write the label for this, or just have the PET level for the amyloid pathology and ignore the tau? What's the thinking on this?

DR. BURACCHIO: Hi. Teresa Buracchio. The population that was enrolled was a population that met clinical criteria for -- well, in our guidances, we refer to them as stage 3 and stage 4, but the common parlance would be mild cognitive impairment or mild dementia with the presence of

amyloid confirmation, indicating that these stages are due to Alzheimer's disease. So what we would think about for labeling is labeling it based on the clinical syndrome that was being presented with mild cognitive impairment and mild dementia.

Currently, in other products that we have labeled, we have noted in Section 2 of the dosing information that confirmation of amyloid pathology is required for treatment or should be checked before treatment; so I would anticipate we would have similar recommendation in this stage since they did confirm amyloid pathology, and amyloid pathology would be necessary for the diagnosis of Alzheimer's disease.

DR. MONTINE: Nilufer?

DR. ERTEKIN-TANER: Nilufer Ertekin-Taner. I have a clarifying question regarding exclusion criteria based on microhemorrhages. Were there any? I thought I heard over 4 microhemorrhages were excluded from the study; is that right?

DR. BURACCHIO: Hi. Teresa Buracchio. That is correct.

DR. ERTEKIN-TANER: Okay. So superficial siderosis, they weren't excluded, but over 4 microhemorrhages were excluded from the study; is that correct?

DR. BURACCHIO: There could be one site of superficial siderosis or up to 4 microhemorrhages. If they had more than one site of superficial siderosis, they were excluded; if they had more than 4 microhemorrhages, they were excluded.

DR. ERTEKIN-TANER: Thank you.

What were the characteristics of those 4 patients who died because of ARIA? There was information on one that was given thrombolytic, but what about the others in terms of their CAA APOE ε4 and superficial siderosis?

DR. BURACCHIO: One second; let me check to see if we have that on the slides.

(Pause.)

DR. BURACCHIO: They don't have that information handy. I don't know if the sponsor might have that.

DR. HYMAN: We can bring it up if you'd

like. If you'd like us to narrate, Melissa Veenhuizen, can I invite you to the microphone to answer this committee member's question?

DR. ERTEKIN-TANER: It would be great if you can narrate, please.

DR. VEENHUIZEN: Melissa Veenhuizen, Eli Lilly. So if you look on the first row with the ARIA-H, that patient did have a baseline superficial siderosis that was greater than 50 millimeters, and they presented with symptomatic headache after the second donanemab infusion. When you look for the rest of the group, you can see that the pathology was not present, except for one individual in the third row with the death to ARIA-E and ARIA-H. This patient actually had multiple episodes of ARIA-E and H that stabilized. This patient was then rechallenged, but at the time of rechallenge, they had 23 microhemorrhages, and then later that was fatal after the 10th infusion.

DR. ERTEKIN-TANER: So the number of microhemorrhages is not shown here; correct?

DR. VEENHUIZEN: For that patient, it is

not; that's correct.

DR. ERTEKIN-TANER: Nor for the others, unless I'm not --

DR. VEENHUIZEN: Correct. Quantitatively, we did not include all of that information on this slide.

DR. ERTEKIN-TANER: Okay. But they would have been less than 4.

DR. VEENHUIZEN: Correct.

DR. ERTEKIN-TANER: Thanks.

DR. MONTINE: Merit?

DR. CUDKOWICZ: I had two questions, the first one on safety for slide 31. It's a clarifying question. Antiplatelet agents or antithrombotics, there was no difference in the risk of the hemorrhages, but it's more the concern of actually thrombolytics. It's less clarity. But as far as physicians feeling comfortable with giving their patients antiplatelets, or Eliquis and that kind of stuff, the safety data is supportive? I may need some clarification on that.

DR. BURACCHIO: I'm sorry. I couldn't hear

you very well.

DR. CUDKOWICZ: Oh, sorry. I was just trying to compare slide 31 to 33, the conclusion. The use of antiplatelet drugs or antithrombotics in the clinic, the safety data, there was no real difference between the groups and risk of ARIA-H; it's more the concern of the IV thrombolytics, more the acute treatment, where there's more uncertainty about the risks.

DR. BURACCHIO: With regard to the antiplatelet agents, the majority of patients were taking aspirin who were taking those therapies. We have smaller numbers of patients who were taking anticoagulant drugs, and we don't see that there is a risk with those therapies in the incidence of ARIA-E or ARIA-H. The risk would primarily be a concern of not whether they develop ARIA-E or ARIA-H, but whether they then have bleeding events, intracerebral hemorrhage in the setting of those due to the risk of background antithrombotic use.

Then the use of thrombolysis, we only have a limited amount of data on the use of thrombolysis.

We have this case that we reported, and there have been a few other cases reported in the literature. Overall, they're negative reports. We don't have reports of patients who may have gotten thrombolysis and done well because they haven't been reported as SAEs, so there is a bit of a bias that we've received reports of. It will be very important in a postmarketing setting to characterize the use of thrombolysis in patients who are receiving these drugs so that we can see if there are other situations where patients are receiving the thrombolytics and are doing well.

So I think, overall, we still have some uncertainty. With regard to the use of antithrombotics and antiplatelets specifically, we don't see an increased risk of intracerebral hemorrhage or ARIA with the use of aspirin. The numbers of antithrombotics/anticoagulants, is very small, and the number of thrombolytics is even smaller.

DR. CUDKOWICZ: Thank you.

My other question is about slide 16 for

Dr. Krudys, if I can say your name correctly. I was trying to figure out people who went to placebo because their amyloid stayed in the long-term extension on placebo, in which case will we eventually be able to get to this question of do you need to restart the drug or not?

DR. KRUDYS: Kevin Krudys. So the question is, patients who switched to placebo, did they stay on placebo when they went to a long-term extension?

DR. CUDKOWICZ: Yes.

DR. KRUDYS: Yes, they did, and I think we should have that data in the future to follow up to see how they progressed and the amyloid levels; we don't have that now, though.

DR. CUDKOWICZ: Okay. So the 29 percent that you have on your slide are people who are still on the drug who didn't achieve this?

DR. KRUDYS: It's patients who are in the treatment arm who decided to go into the extension study, who were still on the 1400 dose.

DR. CUDKOWICZ: Okay. Alright. Thank you.

DR. CARLSSON: Cindy Carlsson, Wisconsin. I

had a question both for efficacy and for safety. I know the FDA is increasingly scrutinizing the diversity of participants in these studies and that there is fewer than 3 percent African American in this study and just two Native American. It looked like a lot of the Hispanic Latino were excluded, and African American, because of the amyloid tau levels, but with the low numbers there, does FDA have any concerns whether the study meets their criteria for diversity to make these recommendations across populations that will be at risk for dementia and potentially interested in receiving the drug?

DR. BURACCHIO: Hi. Teresa Buracchio. Well, this is a therapy that's targeted to amyloid, and presence of amyloid was required for enrollment in the studies and is generally recommended for treatment of these patients. So to the extent that individuals who might be prescribed to therapies are being screened for amyloid, we have no reason to think that there'd be a difference in the effect of the drug in reducing amyloid. The clinical

benefit may differ, that is observed, and may differ across different racial ethnicities given that there's a difference in comorbidities that may be present in different groups.

So we can say that we believe the drug would work based on reduction of amyloid. The degree of clinical benefit may be more difficult to generalize across different populations; however, we do typically describe the treated population in Section 14 of our labeling, and more work certainly needs to be done on improving diversity in our trials and understanding the benefit that might be seen across these drugs across the population.

DR. MONTINE: Thank you.

Costantino?

DR. IADECOLA: Costantino Iadecola, Weill Cornell. I was wondering, is there any data on the atrophy post-treatment in these patients? And the other question is, is there any data on the efficacy with respect to the overlap to small vessel disease? People with Alzheimer's will have also overlapping muscular pathology. What kind of

a determinant is that of the efficacy of the treatment?

DR. KRUDYS: For the first part of the question, yes, we did see changes in brain volume. We saw a decrease in total brain volume, I believe, and increase in the ventricular volume, which is consistent with what we've seen for drugs in the class. I could speak to that, and then Teresa could speak to the second part.

DR. BURACCHIO: Yes. Teresa Buracchio. As part of the screening for inclusion and exclusion, I believe that there was some consideration taken into the white matter hyperintensity burden. I actually might ask the applicant if they could comment on that.

DR. SIMS: John Sims, Head of Medical. Indeed, stage 3 Fazekas scores, those people were excluded from the trial, and beyond that, it's hard to say the impact of small vessel disease. No other kinds of strokes were excluded, but stage 3 Fazekas was excluded.

DR. IADECOLA: Inasmuch as small vessel

disease can be indicative of CAA, that may be an important consideration for determining thrombolysis or other emergency treatments that may be needed. The people who died, they all went to the ER for something else, and they were not, obviously, prepared to deal with these patients.

DR. BURACCHIO: Yes, I agree it will be important to understand the co-pathologies that are present on imaging and the role that they play. I think that will be important in a post-approval setting to better characterize this in the registry. We have had postmarketing requirements for other drugs in this class for a registry to look at MRI; we would consider having a similar postmarketing requirement in this setting.

Dr. Yasuda, would you like to speak to the -- I can't remember the language we've used in other postmarketing.

DR. YASUDA: The postmarketing requirements for the other drugs, and most likely for this as well, look at deaths, serious adverse reactions, ARIA-E, ARIA-H, and also use of concomitant

therapies and MRIs, and hopefully will be comprehensive and help us learn more about all of this.

DR. MONTINE: Thank you.

Tanya?

DR. SIMUNI: Tanya Simuni, a clarifying question regarding generalizability of the population recruited into the study versus the population that is being seen in the clinic; slide 5, Dr. Krudys, and probably the applicant would have more data.

So there were 8240 patients screened versus a little bit over 1700 enrolled, which is 20 percent of the screened population that qualified for the study. What were the major criteria for screen failure categorically? And again, probably the applicant --

DR. BURACCHIO: The applicant did have a slide on this earlier, if you would be able to show that again.

DR. HYMAN: Absolutely, happy to. This is screen failure rates. The primary reasons for

screen failure were absence of amyloid pathology, so I think appropriately we don't want to be enrolling patients that don't have Alzheimer's disease is the cause of their dementia; then also, too severe symptomatic disease as measured by MMSE.

DR. SIMUNI: Thank you very much for bringing that back. Thank you.

DR. MONTINE: Nilufer?

DR. ERTEKIN-TANER: Nilufer Ertekin-Taner. Patients with more than 4 microhemorrhages, superficial siderosis in more than 2 areas, and we recently heard stage 3 physicus, were excluded from the study. So a clarifying question to the FDA, what is your perspective of how to take that into consideration in the information? Are these contraindications, relative contraindications, warnings? What is the FDA's perspective?

DR. BURACCHIO: Hi. Teresa Buracchio. These have been used as exclusion criteria in the studies; however, we are also aware that during the course of the studies, although these were things that were done at baseline, there were participants

in the studies who went on to develop additional microhemorrhages during the course of the study who may have developed other areas of superficial siderosis, who continued to do well with therapy despite developing new findings on MRIs.

We have a hard time saying that this would be an absolute contraindication because even though it was at baseline, we do note that there have been other participants who have been able to be dosed with these therapies. We have in our labeling for other products noted that these criteria were used largely as a way of identifying individuals who are at risk for CAA, and then who might therefore be at an increased risk of intracerebral hemorrhage; and we have noted that in labeling, but we haven't made that an absolute contraindication. It's more of an informative practice for prescribers to consider these as risk factors for intracerebral hemorrhage in the population.

DR. ERTEKIN-TANER: Then with respect to thrombolytic use, is there any thought on the language to utilize during the donanemab usage, as

well as afterwards in terms of the thrombolytic being a contraindication?

DR. BURACCHIO: Well, I think it's difficult to make a thrombolytic a contraindication because it is used in the setting of an acute onset of new symptoms, so it would be in a setting of somebody who is already being treated with donanemab who develops new symptoms and presents to an emergency care facility. I think it would be up to the prescriber to weigh the severity of the stroke.

If you had a very severe stroke with a major vessel, a large vessel stroke that was causing significant morbidity, you're between a rock and a hard place. You're going to have a difficult time as that prescriber figuring out the right thing to do for that patient, and it would be hard for us to say don't treat with thrombolytics in those situations. It's more for us to try to educate the prescribers so that they are aware of these risks, but they will ultimately have to make that decision in talking with the patient, the family, and the care providers that are available to help provide

consent for treatment, but in the labeling, we would certainly describe that.

Also, I will say, as I noted, that even though we have seen a few bad events now with thrombolysis, there is a bias to the reporting of those events; that we don't know if there's been successful treatments of events that haven't had bad outcomes. So even though in the setting of having seen these bad events, it's still really difficult for us to say that they are definitively due to the drug. I think right now we're in a situation where we're urging caution with the use of thrombolytics, careful consideration by the prescribers of the risks and benefits of using thrombolysis in patients who are presenting with acute neurologic deficits.

Dr. Yasuda, would you like to add to that?

DR. YASUDA: This is Sally Yasuda. I just wanted to add the part of the educational part of the label will be also to make sure that people are aware that the symptoms of ARIA can mimic symptoms of stroke.

DR. MONTINE: Kathleen?

DR. POSTON: Thank you. In light of the almost 25 percent of individuals who were screened out due to a negative amyloid scan, what was the criteria for that? Was it visual reads, centiloids, combination; and how is the agency thinking to translate that to amyloid positivity being interpreted from a labeling perspective?

DR. KRUDYS: Kevin Krudys here. So they had a requirement for a centiloid threshold to be enrolled of 37, and I think the idea was to ensure that patients had to target for treatment. I think for labeling, we wouldn't require a threshold. We would just say a positive scan, or a positive CSF, or plasma, whatever.

DR. BURACCHIO: And I'll just also note that the labeling for imaging, and for amyloid PET imaging agents, and tau PET imaging agents are handled not by our division, but our Division of Imaging and Radiographic Medicine, and we are working with them and discussing issues with them about whether there would be impacts on the

labeling of those diagnostic agents.

DR. MONTINE: Tanya?

DR. SIMUNI: I had a question regarding categorical approach to definition of amyloid positivity versus specific biomarker, but I think Dr. Krudys has just answered that. So just to clarify, it sounds like if the drug is approved, it will be categorical amyloid positivity and not just bad imaging, which was done by the applicant, but CSF plasma biomarkers of amyloid positivity will be approached categorically.

DR. BURACCHIO: Hi. Teresa Buracchio. Based on the presence of amyloid, in order to use one of these drugs, we have available approved amyloid PET imaging agents and also CSF tests. As you've heard, there are emerging plasma-based biomarkers, although none that have been approved by the FDA yet.

A categorical use of the amyloid PET imaging agents or the CSF tests would be adequate to inform presence of amyloid to initiate a therapy; however, if we were to consider the dosing paradigm of

possibly stopping dosing based on amyloid PET -- the applicant did use a quantitative cutoff for that threshold, but it appears that that threshold is roughly consistent with a visual read of a negative PET scan. So it may be possible to use a PET scan just as a visual read of positive/negative to stop therapy if that dosing regimen were to be considered as a reasonable approach.

DR. MONTINE: Dean?

DR. FOLLMANN: Dean Follmann, NIH. This is a question for Dr. Krudys. He mentioned that about 29 percent of the people in the mab arm continued dosing into the open-label phase, so they'd been on mab for over a year and they can continue. Was there a sense of, at some point, maybe we should just stop because things have stabilized and there's no hope for improvement on the biomarker, or was the plan to just continue for years and years on those?

DR. KRUDYS: Kevin Krudys. I don't think we have looked exactly where their status is at the

end of the study in terms of plaque reduction. I think the idea is to continue on the drug for those patients who haven't hit that threshold yet. As you heard in the morning from the sponsor, we do see in the trial that all patients do appear to have a reduction in amyloid plaque, so it's not just some. So it's possible that there are some that are slower and may take a bit longer to reach that threshold.

DR. FOLLMANN: Or maybe some that will never reach the threshold and just continue on unless there is the drug is stopped. I guess we don't really know --

DR. KRUDYS: We don't have the data, but it's possible that that could be the case.

DR. FOLLMANN: Yes.

DR. MONTINE: Cindy?

DR. CARLSSON: Cindy Carlsson. Just to clarify on the previous question about what biomarkers can be used for treatment, if CSF is used, would they have CSF follow-up to see -- if CSF is used to qualify for having elevated amyloid,

positive or negative, would CSF be able to be used to stop therapy given that CSF is kind of confusing because it actually is reciprocally related to amyloid PET scans?

DR. BURACCHIO: Yes. I think the CSF is a more challenging question because we do know that amyloid PET was used in the clinical trials. We don't have experience with using CSF levels to inform dosing recommendations; however, again, as we would say with the amyloid PET, if you could take qualitatively as a positive/negative, we could do that potentially with PET to inform dosing. I'm less certain if that approach would be useful with CSF, but it is something that could be considered and perhaps investigated further, whether a qualitative assessment of CSF reads could also be used.

DR. CARLSSON: Because it's more widely available, obviously, in rural regions and things, but I think it'd be more difficult to interpret.

DR. BURACCHIO: Yes.

MS. DOLAN: Sarah Dolan. I have a question

about age restrictions. In the study, the average age was 73 years old of the participants and ages 60 to 85. Would anyone that meets this proposed indication -- all comers -- be authorized or able to use this medicine?

DR. BURACCHIO: Hi. Teresa Buracchio. For labeling for drugs, we typically have a broad categorization for use in adults, and we typically, at least for adults, don't often have age cutoffs in labeling unless there was a specific safety concern to indicate that a drug might be unsafe in a particular population. It would be informative, and that's usually probably more of a concern at the higher end of the age range than in the lower end of the age range, but I think we did still see that there were overall trends of benefits in patients less than 65.

MS. DOLAN: Right. I'm thinking there could be a few younger patients that would qualify for this.

DR. BURACCHIO: Yes.

MS. DOLAN: Okay.

DR. MONTINE: Costantino?

DR. IADECOLA: Concerning the use of thrombolytics, I wanted to point out that there is an increased risk of brain hemorrhages in people getting PPA or CAA. So conceivably, if CAA increases the risk of ARIA, the risk of brain hemorrhage may not be different than the patients who have CAA. So perhaps that should be taken into consideration in your deliberations.

DR. BURACCHIO: Yes, thank you. That is something that we have also thought about, and it just makes it that much more difficult to interpret some of this data and to say that there is a clear risk with the drug.

DR. MONTINE: May I ask FDA's opinion, the possibility of unblinding because of ARIA?

DR. KRUDYS: Kevin Krudys. I suppose I would say similar to what the applicant said in the morning. There were steps in the protocol to address the potential for that. As they had mentioned, people who were involved in the study who were doing the trial were blinded to whether or

not the patient had an event. So that was one thing to do before the study, and then we looked at the analysis that was presented in the morning as well, looking at excluding patients, or excluding data post the event to see if that changed the estimate, and we didn't see a big change. So for those two reasons, we think there's probably not a large effect of unblinding.

DR. MONTINE: Thank you. And if I could ask a clarification, how you imagine a suggestion or a requirement around APOE ε4 status if you were to approve this drug?

DR. BURACCHIO: This is Teresa Buracchio. We've had some discussion around this, particularly with the other available therapies that APOE ε4 homozygosity does seem to be a clear risk factor for ARIA, and in the presence of a single allele is a bit of a risk factor as well but not as significant as homozygosity.

We have a recommendation, although I'd say it's a strong recommendation, to test for APOE ε4 genotype status with the use of these drugs to

inform risks. One reason that we haven't made it a requirement is with regard to other implications for genetic testing.

We don't feel that it would be -- in doing this genetic testing, you're also categorizing risk for disease, which might have implications both for the patient and other care -- health insurance, other care that they may get -- and also for their relatives. So we still have a challenge in saying it should be required because we want to leave that up to an individual's discretion if they have concerns, privacy concerns, or how it might impact other aspects of their life; that they have that freedom to decline. If they do, we most likely need to assume that they are at the higher level of risk that a homozygote would be at, but we would strongly recommend it in order to have that informed discussion between prescribers and patients.

DR. MONTINE: Great. Thank you.

Daniel?

DR. PRESS: Dan Press. Following up on the

ε4 homozygosity, the other end of it is the question about efficacy in ε4 homozygotes. I've seen some data, but not all. It's admittedly a small subgroup, but this is now the second trial where there's been a question around efficacy and ε4 homozygotes. I'm wondering what you think about that.

DR. BURACCHIO: Hi. Teresa Buracchio. As I just noted, it is a small subgroup, so we have the usual caveats around subgroup analyses and small subgroups. I think the question that was raised on the slides from the applicant's presentation regarding whether there might be less exposure to the drugs in these patients is a good one that we haven't been able to fully interrogate yet. I think this would be a rather complicated modeling to look at, but I think it would be informative if we could.

Because homozygotes are at an increased risk of ARIA, they're also having their doses paused more than other patients, and the amount of time that that dose is being paused can be quite

variable. We have looked at the duration of a pause, and it can be as little as a month or two, up to 6 months or more, so I would have to think that that could have some impact on the efficacy that we're seeing, although we don't have any quantitation, actually, to quantify that effect.

DR. MONTINE: Nilufer, please.

DR. ERTEKIN-TANER: Nilufer Ertekin-Taner. Autosomal dominance, Alzheimer's disease patients and patients with Down syndrome are special categories of patients. Can you inform us about the inclusion or exclusion of these patient categories and whether there are any FDA relevant recommendations that you plan to include?

DR. BURACCHIO: Hi. Teresa Buracchio. So yes, we recognize the prevalence of Alzheimer's disease in patients with Down syndrome and agree that it's an important population to understand how these drugs would work. Based on the comment I made earlier, that these are drugs that are targeted to amyloid, the presence of amyloid would need to be confirmed and is likely to be present in

these Down syndrome individuals. We do think that the effect on amyloid should be similar to the sporadic Alzheimer's disease patient population; we would expect that.

Whether there might be other factors that would impact the degree of clinical benefit might vary, and given also what we know about homozygosity with APOE ε4, safety could be a little different in these patient populations as well. So I do think it would be important to have data in these populations that we could compare to the sporadic population that has been included in these studies, but we are not able to require those sorts of studies be done. We would just recommend that those sorts of studies be done.

I see the applicant is standing up, so perhaps you could tell us about any plans you might have.

DR. HYMAN: [Inaudible - 3:55:16]

(Pause.)

DR. BURACCHIO: I will also just add, while we're waiting, that it is difficult to include

these individuals with Down syndrome into the ongoing studies because they would have a different cognitive baseline than the general population that's being enrolled, and they may need different endpoints. So we don't have a good understanding yet of whether the same clinical endpoints -- or at least clinical outcome measures for cognition could be used in the same population.

DR. HYMAN: Hopefully this works now.

David Hyman from the sponsor. We indeed recognize those are two very important populations that were not addressed in our pivotal program. We actually have academic industry collaborations planned for both of those populations, with two unique studies that we plan to launch in the near future to address that data gap.

DR. MONTINE: We have about 20 minutes remaining in this session, so, if possible, I'd like to return to questions we have for the sponsor that we didn't get to in the previous session.

Dr. Hyman, if you would please?

DR. HYMAN: If it would be ok, we're still

working on those responses. If we could come back to them, potentially, after the --

DR. MONTINE: Well, we have at least one additional question.

DR. HYMAN: Oh, one additional -- oh, I'm sorry. I thought you meant responses. Oh, we're happy to take additional questions.

DR. MONTINE: If I may, just to clarify, I'm not sure how much time we're going to have this afternoon --

DR. HYMAN: Okay.

DR. MONTINE: -- so if possible, we can get to as much as we can in the next 20 minutes, and if possible, we'll have time after lunch, but I can't promise the time after lunch.

DR. HYMAN: Understood.

So Costantino, you had a question for the sponsor.

DR. IADECOLA: I was able to get the answer by asking the FDA.

(Laughter.)

DR. MONTINE: Okay.

Any of the data, have you had a chance to get to any of this? I know it's very short notice, but since we have the time.

DR. HYMAN: We did give the assignments during the 15-minute break. I haven't been able to see any of them yet. They're not coming on my prompter, so I can't answer them right now. I apologize.

DR. MONTINE: Please don't apologize. The timing is very short.

Daniel?

DR. PRESS: I'd like to follow up on a question to the FDA on efficacy and ε4 homozygotes. I think it was in the CDR sum of boxes where you showed it. Have you looked at other measures to see if there's evidence of efficacy in them? Admittedly, it's a small group, but because they have a higher safety burden as well, it's of particular importance clinically.

DR. HYMAN: Absolutely. We fully understand. In fact, in our phase 2 study, which we haven't spent the majority of today talking

about, in that subgroup, we actually had the highest levels of efficacy in that subgroup, albeit a much smaller study, and then proportionally a smaller subgroup. So if we look at the program in totality, we don't see strong evidence of decreased efficacy in that subgroup, with the important caveat that the study was not powered to detect the efficacy specifically with precision in that subgroup.

DR. MONTINE: Cindy?

DR. CARLSSON: Cindy Carlsson. Going back to the question about whether CSF could be used, which again is more widely available in different areas, did the study collect CSF in a subgroup of participants to look and see what happened to the changes in amyloid levels?

DR. HYMAN: In designing the study, we did try to minimize the extra burden on participants. We didn't collect serial CSF analysis, and as such, we wouldn't be able to provide data-driven guidance about the use of CSF clearance for cessation of the treatment.

DR. CARLSSON: Thank you.

DR. MONTINE: First, thank you. I didn't mean to put you on the spot.

DR. HYMAN: No. We're happy to answer all questions that you have.

DR. MONTINE: If this is ok with the group, questions are done for the FDA. We've finished 15 minutes early. We're going to break for lunch 15 minutes early, come back 15 minutes early, and have 15 minutes, but that'll be it, after lunch.

Will that work for you?

DR. HYMAN: Absolutely. We'll bring them back. Thank you.

DR. MONTINE: Great.

So it's now just 12:30. We're going to reconvene at 1:15 with the sponsor for 15 minutes, and then back on the agenda.

Thanks, everyone.

(Whereupon, at 12:30 p.m., a lunch recess was taken, and meeting resumed at 1:18 p.m.)

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

(1:18 p.m.)

DR. MONTINE: Hello, everyone.

Dr. Hyman, would you like to begin?

DR. HYMAN: I think there were two questions that we were asked that we caught during our original question/answer session that I wanted to return to and have an opportunity to address, and thank you for the opportunity to do so.

The first was about the distribution and safety findings within two underrepresented minority populations, Black patients and Hispanics by APOE status. And just to orient you before I go to that question specifically, we do have safety by the All Dona population, as well as by Black or African Americans and Hispanics, and overall, I'll let you peruse those tables, but you can see that the safety findings in those populations are largely consistent.

Can I have the next slide in the series? It's, I think, AA-3.

To answer the question directly, this table

shows you within the Black and African American population, which was 24 patients in the placebo-controlled period. This breaks out the safety findings by APOE genotype, the homozygotes, heterozygotes, and non-carriers. Obviously, these numbers are small, but broadly speaking, there appear to be slightly increased risk, as one would expect, with increasing gene dosage of the APOE status, broadly consistent with the overall population.

Next, I'll turn to the same table, but this time for the population of Hispanic patients enrolled, 40 patients total, during the dona placebo-controlled. Again, you can see the distribution here of APOE carrier status is similar to the overall study population and, again, I think you can appreciate perhaps a slightly increased risk of ARIA in the APOE ε4/4 homozygotes, again, consistent with that in the broader population.

The next question that we got was in regards to whether the APOE status itself, and specifically within homo or heterozygotes, could increase the

risk of functional unblinding and impact the interpretation of the study results. So I want to answer this in two parts. The first is, I just wanted to show you the CDR sum of boxes in the overall population and with the preplanned censoring analysis at the first event of ARIA.

On the left, you see the overall study population with 29 percent slowing by CDR sum of boxes with no censoring. When the censoring rules would applied at the first occurrence of ARIA-H or ARIA-E, in the overall study population, you see nearly identical results in both the absolute degree of slowing as well as the relative degree of slowing, but to answer the question directly, I'll pull up this table.

What we're showing here is the carrier status in columns with non-carriers, heterozygotes, and homozygotes. We wanted to show you the results with no censoring applied within the subgroups, and then with censoring applied within the subgroups. You can see that within the non-carriers, and now in this column we're excluding heterozygotes or

homozygotes from the analysis, and you can see that within the non-carrier population, with censoring applied or no censoring applied, the relative slowing is nearly identical.

Again, within the heterozygotes population, which is the largest population in the clinical trial, the treatment difference on both an absolute and relative basis is nearly identical with or without censoring. And finally, within the APOE 4/4 homozygotes, you can see directionally similar relative benefit with or without censoring.

An important caveat here is that when you now apply censoring to an already small population, you're left with a very small number of patients, and the precision of that point estimate is obviously quite broad. But overall, we hope this provides reassurance that the APOE status didn't lead to selective unblinding that interfered with the interpretation of the study results.

DR. MONTINE: Thank you very much.

We have time for one or two follow-up questions.

(No response.)

DR. MONTINE: Great. Not hearing any, I'll thank you again, you and your team.

DR. HYMAN: Thank you.

DR. MONTINE: And, Dr. Buracchio, you wish to make a comment.

DR. BURACCHIO: Hi. Teresa Buracchio. I just wanted to follow up on a question that we had earlier about the recommendations regarding APOE ε4 genotype testing. We do have class language that we've used for ARIA risk, and there is a boxed warning for the risk of ARIA, so I just wanted to let you know what we currently have in our class labeling. This also can be updated subject to change. We do review these things periodically as new safety data becomes available and update them.

As it currently reads, "Testing for APOE epsilon 4 status should be performed prior to initiation of treatment to inform the risk of developing ARIA. Prior to testing, prescriber should discuss with patients the risk of ARIA across genotypes and the implications of genetic

testing results. Prescribers should inform patients that if genotype testing is not performed, they can still be treated with the drug; however, it cannot be determined if they are APOE epsilon 4 homozygotes and at a higher risk for ARIA."

We also do have a note that there is no FDA approved test for APOE ε4 genotype testing currently. There are lab-developed tests that are available and are widely used; however, there is not one that's approved by the agency yet, so there may be variability in the results that have to be considered when using those tests.

DR. MONTINE: Thank you very much.

Any follow-up comments for Dr. Buracchio?

(No response.)

Open Public Hearing

DR. MONTINE: Well, thank you again.

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, the FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the committee of any financial relationship that you may have with the applicant. For example, this financial information may include the applicant's payments for your travel, lodging, or other expenses in connection with your participation in the meeting. Likewise, FDA encourages at the beginning of your statement to advise the committee if you do not have such a financial relationship. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

The FDA and this committee place great importance in the open public hearing process. The insights and comments provided can help the agency and this committee in their consideration of the

issues before them.

That said, in many instances and for many topics, there will be a variety of opinions. One of our goals for today is for the open public hearing to be conducted in a fair and open way, where every participant is listened to carefully and treated with dignity, courtesy, and respect;, therefore, please speak only when recognized by the chairperson. Thank you for your cooperation.

Those who are about to speak in the open public hearing session, you are provided three minutes to make your comments. We have speakers organized who will fill the entire time allotted, so I'm going to need to ask the AV team to mute the speaker once the three minutes is over, so please contain your comments to three minutes or less.

Speaker number 1, please unmute and turn on your webcam. 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.

MR. CLINTON: Thank you. My name is Dan

Clinton. I'm a registered nurse from Massachusetts, and I have no conflicts of interest. Donanemab is neither safe nor effective, and its administration unethical, paradoxical, self-defeating, and both morally and scientifically wrong.

Donanemab in its phase 3 study killed 1 in 285, was associated with a non-statistically significant 65 percent increase relative risk of death, caused symptomatic brain swelling in 6.1 percent, 13.5 percent of whose symptoms did not resolve; therefore, the drug killed or permanently disables greater than 1.2 percent. It caused 13.1 percent to discontinue treatment due to an adverse event versus 4.3 percent placebo, and caused serious amyloid-related imaging abnormalities, a euphemism for brain swelling and hemorrhaging, in 1 in 67; thus, donanemab is unsafe.

Donanemab caused brain swelling in 24 percent; brain bleeding in 20; 1 in 12 with an infusion-related reaction; 1 in 200 with

anaphylaxis greater than 5 times the rate of superficial siderosis; 1 in 16 with symptomatic brain swelling; and 1 in 122 with serious brain damage that did not resolve. A drug associated with a 65 percent increased risk of death that kills 1 in 285 and permanently destroys irreparably more than 1 percent of brains is unsafe in an objective reality.

Three lives were lost at donanemab. Beyond being inherently unsafe, donanemab was proven ineffective. Of the 860 randomized to donanemab, only 622 completed the study and were included in final analysis, so those who withdrew their consent experienced an adverse event, were withdrawn by their physician or died were not included; so any purported efficacy is an artifact of attrition or survivorship bias.

The neuro status of those randomized to donanemab is almost certainly worse than those randomized to placebo. That's just been obscured by the duplicitous way which the results were presented. Donanemab's purported efficacy was a

tiny, absolute slowed rate of descent on questionnaires. The survivors scoring 3 points better on a scale from 0 to 144 after 17 IV infusions, 2 PET scans, and 5 MRIs does not constitute efficacy.

Here on the left, you can see the way donanemab's purported efficacy was presented. On the right, I've rescaled it from the actual starting point to the actual endpoint shown on the actual scale, and this isn't even a real effect because of purification by attrition. But even if it were, it is not disease modifying, clinically perceptible, or indicative of anything resembling meaningful efficacy.

Seventy-six percent of patients achieved amyloid clearance, yet the donanemab group still declined neurologically at a rate of 7 percent for 76 weeks. Additionally, 48 percent of patients who achieved amyloid clearance failed to achieve a meaningful within-person change. These non-correlations disprove the amyloid cascade hypothesis.

Amyloid is neither necessary, sufficient, nor specific for dementia. Amyloid fails Koch's first --

DR. MONTINE: Thank you, speaker.

MR. CLINTON: -- and third postulate.

DR. MONTINE: Thank you, speaker. Your three minutes have ended.

DR. CLINTON: Thank you.

DR. MONTINE: I'll ask the AV team to please mute the speaker.

Speaker number 2, please unmute and turn on your webcam. Will speaker number 2 begin and introduce yourself? Please state your name and any organization you represent for the record. You have three minutes.

MS. BISHARA: My name is Pat Bishara. I am a donanemab clinical trial patient. In terms of disclosures, my husband, Rafik Bishara, who is sitting next to me, retired from Eli Lilly 20 years ago but never worked in anything related to Alzheimer's development.

I personally worked for Eli Lilly for less

than one year way back in 1968. I shared my story at the Indiana Chapter and the Chicago Chapter of the Alzheimer's Association 2024 fundraising events, both of which raised funds' record this year; however, my testimony today has nothing to do with that. I am not being reimbursed for my testimony today by anyone.

I was diagnosed with Alzheimer's in December 2017. I just had my 41st and last infusion last Thursday, June 6, 2024. It has been nearly seven years since I was diagnosed. Usually by this time, people who have been diagnosed would have more symptoms. I can still drive, play bridge, live independently, create new memories with my grandchildren, and take communion to people who could not get to church. Despite being diagnosed almost seven years ago, I am still able to drive to get together with friends, and I try to go to daily mass.

I speak English, Spanish, and some French. I fear the day that I will no longer be able to drive and will have to start to depend on others to

take me to where I want to go. Throughout these seven years, I have not declined much. My family and friends would agree that I am still functioning at a high level. Those who do not know that I've been diagnosed with Alzheimer's may not even realize that I'm dealing with this disease.

So many people don't want to tell others they've been diagnosed with Alzheimer's. It's not contagious, and it isn't anything to be ashamed of. It's so important to see a doctor as soon as you can. The reasons that I'm doing this so well is because I saw a neurologist for my early diagnosis, and I volunteered as a patient in the donanemab clinical trial. I haven't had any side effects, thank God. I feel so blessed that I was able to get into this study.

I am testifying today because I really want people to know how important it is to get diagnosed and treated early. If you see signs and symptoms, please don't wait too long to meet with a doctor. Please get diagnosed and treated as soon as possible. I wholeheartedly recommend that

donanemab be put on the market so it is available to others and me. Thank you, and God bless you.

DR. MONTINE: Thank you, speaker.

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

MS. SIROIS: Good afternoon. My name is Sue Sirois. I want to thank you for allowing me to speak today and share my husband Jim's story, who is currently living with Alzheimer's disease. But before I do, I want to first mention that I have no financial interest and I'm not being compensated for my time today. I just want to share my husband's story with all of you.

Jim was diagnosed in April of 2020 with dementia due to what doctors thought was a combination of vascular and Alzheimer's disease at the young age of 64. As you can imagine, we were shocked and devastated by this news, especially because there's no cure. I think the most

unfortunate thing is that Jim's diagnosis was right in the middle of the pandemic. Our doctor suggested that Jim try to qualify for a clinical trial, but all clinical trials stopped during the pandemic and, unfortunately, during that first year, progression continued at a disturbing rate.

Knowing nothing about Alzheimer's disease, I started reading and educating myself as much as possible about what to expect, and one of the most disturbing things that I learned was that the average lifespan for someone with Alzheimer's disease was a mere 8 years. We needed more time.

In November of 2021, Jim finally qualified for the TRAILBLAZER-3 trial, and Alzheimer's disease was confirmed as a result of the PET scan. Jim decided to join the clinical trial not only to help research and help people in the future, but to selfishly try to slow his own progression. Jim started getting infusions of donanemab in this 18-month trial. He did very well with the infusions with no real side effects to speak of.

In January of 2023, his infusion stopped

because the amyloid plaque was sufficiently removed from his brain based on the results of a PET scan. Even though Jim really didn't have any side effects as a result of the medication, it was a relief to us that the infusions can stop after the marker has been met. The trial officially ended in June of 2023.

We are now four years into this disease, and I can honestly say that Jim is still doing ok. His progression is still happening but ever so slowly. It seems that every year there's a little more he can't do. We have had to make significant changes in managing our households. Our life is very different now, but we still enjoy life to the best of our ability, and Jim is still here.

Donanemab is not a cure, but my gut feeling is that the medication has slowed Jim's progression and has given us more time as a family. I only wish that Jim had been able to get into the clinical trial sooner than he did before further progression occurred. So I sincerely ask the FDA to approve this medication for people suffering

from this disease. This is a real hope that people have, and every month that we can have with our loved ones is precious for families. Thank you so much for your time.

DR. MONTINE: Thank you, speaker.

Speaker number 4, please unmute and turn on your webcam. Will speaker number 4 begin and introduce yourself? Please state your name and any organization you are representing for the record. You have three minutes.

DR. PIKE: My name is Joanne Pike. I am the President and CEO of the Alzheimer's Association. The Alzheimer's Association received 1.29 percent of its total 2023 contributed revenue from the biotechnology, pharmaceutical, diagnostics, and clinical research industry, inclusive of 0.18 percent from Eli Lilly. This and additional information can be found at alz.org/transparency. 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 donanemab, an anti-amyloid treatment that reduces cognitive and functional decline in individuals with early Alzheimer's disease. In the Alzheimer's Association written statement, we present a comprehensive review of the case for recommending to the FDA that it grant approval for donanemab. In my remarks today, I would like to emphasize three points from that submission.

First, the published phase 3 clinical trial data regarding donanemab convincingly met the primary and all cognitive and functional secondary endpoints. Numerous data points demonstrate that donanemab has shown a meaningful clinical benefit for patients treated, the culmination of which means that participants treated with donanemab in this population experienced an additional 7.5 months over an 18-month trial.

Second, donanemab has demonstrated significant benefits on important cognitive and functional endpoints, easily meeting the standard

for FDA's traditional approval process. Donanemab's data also demonstrates a significant benefit on a personal level for patients in need of treatments, and the personal meaningfulness to patients, their families, and their caregivers is no less significant as you will also hear today.

Third, we acknowledge that donanemab and all anti-amyloid treatments in this class of drugs have side effects. We are confident that the side effect profile for this treatment is, on the whole, manageable and less dangerous than for many other FDA-approved medications for severe and life-threatening illnesses.

The Alzheimer's Association works closely with the medical and scientific community to better understand ARIA. In March 2024, the Alzheimer's Association established a work group consisting of experts in the field of basic science, neuropathology, neuroradiology, and bioethics to discuss growth, as well as current gaps in knowledge regarding ARIA.

While the work group discussions are

currently ongoing, the preliminary objective is to equip the scientific and clinical community with a comprehensive understanding of the latest knowledge on ARIA, as well as recommend directions for future research. For appropriate patients under the care of clinicians providing proper care and monitoring, ARIA risk is manageable in real-world clinical settings. No barrier should stand between patients and a treatment that has a reasonable risk-benefit ratio and significantly reduces the causative pathology.

Finally, approval of donanemab should not be delayed for reasons related to the duration of treatment, and access to the therapy should not be limited by additional diagnostic requirements. Thank you for your service today and your careful consideration of the evidence before you. We strongly support --

DR. MONTINE: Thank you, speaker,

DR. PIKE: -- the traditional approval of donanemab.

DR. MONTINE: Thank you, speaker. Your

three minutes have ended.

Speaker number 5, please unmute and turn on your webcam. Will speaker number 5 begin and introduce yourself? Please state your name and any organization you are representing for the record. You have three minutes.

DR. ZELDES: Thank you. Good afternoon. I am Nina Zeldes, a health researcher at Public Citizen's Health Research Group. We have no financial conflicts of interest. Public Citizen opposes approval of the biologics license application for donanemab for the treatment of Alzheimer's disease because the evidence for the drug's benefits does not outweigh its substantial risks. The essential issue is the specifics of the prescribing information about whether the drug should be approved to begin with.

In the pivotal clinical trial, there was a statistically significant difference between the donanemab and placebo groups for the primary endpoint; however, the difference in both of the primary endpoint populations was only about

3 points on a scale that ranges from 0 to 144. We view this 2 percent difference between groups as unlikely to be clinically meaningful. The statistically significant differences between the groups and secondary endpoints were also small and of uncertain clinical significance.

In contrast to the weak evidence for clinical benefit, the safety data for donanemab are very concerning. For instance, 36 percent of subjects treated with donanemab developed ARIA compared to 14 percent of subjects in the placebo group. About 24 percent of donanemab-treated subjects experienced more than one treatment-emergent event of ARIA-E, and for approximately 15 subjects, clinical symptoms of ARIA-E did not resolve. At least three of the 19 deaths in the treatment group were associated with ARIA as compared with zero of 16 deaths in the placebo group.

Importantly, the percentage of subjects in the donanemab trial who developed ARIA was higher than in the pivotal trial for lecanemab. It is

very concerning when 21 percent of subjects receiving drug treatment for Alzheimer's disease develop ARIA, as was the case in the lecanemab trial, and even more concerning when 36 percent of subjects develop ARIA, as was the case in the donanemab trial.

Other disturbing treatment effects of donanemab are the increase of ventricular volume and a decrease in whole brain volume. Both of these changes can be associated with Alzheimer's disease progression Additionally, although the prevalence of Alzheimer's disease is higher in black than white individuals, 92 percent of the subjects in the pivotal clinical trial were white.

Public Citizen's Health Research Group opposed the approval of aducanumab, we opposed the approval of lecanemab, and now we oppose the approval of donanemab. We urge the advisory committee to vote no on both voting questions and recommend to the FDA that the biologics license application for donanemab not be approved. Thank you for your time.

DR. MONTINE: Thank you, speaker.

Speaker number 6, please unmute and turn on your webcam. Will speaker number 6 begin and introduce yourself? Please state your name and any organization you are representing for the record. You have three minutes.

MR. O'CONNOR: My name is John F O'Connor. I would like to say I have no financial interest in the Lilly company and I'm not being compensated for my testimony. I'm a 79-year old man who has been diagnosed with mild cognitive impairment. Several years ago, I began noticing a deterioration in my mental abilities. I would have difficulty remembering people's names and birthdays, I would forget some of the items I was shopping for at the grocery store, and I missed several appointments. I also lost the ability to do mathematical calculations in my head. I was managing, but I was declining and fearful of further decline.

I'm familiar with mental impairment since for more than 20 years I was the principal owner of an assisted living facility with a substantial

memory care unit and witnessed the decline of many of our residents. I heard about a research study examining the effects of a proposed new drug to treat my condition. I applied and was accepted. The staff explained the risks and benefits of participating. I have considerable experience in risk-benefit studies and the analysis of risks generally. I'm a trained economist with undergraduate and graduate degrees in economics and have analyzed feasibility studies for the issuance of public bond offerings. On a personal level, I have actively traded stock options for more than 40 years, frequently using complex strategies.

All of these require a deep understanding of risks and benefits. I concluded that the risks of taking the drug were clearly overwhelmed by the possible benefits. A scan on my brain upon entering showed the presence of amyloids. I am pleased to tell you that as a result of the treatment with the Lilly drug, my amyloids have now completely cleared, but this was not an entirely smooth road.

My treatment was uneventful for the first 7 or 8 infusions. During my next infusion, I had an adverse reaction. My right arm began to shake uncontrollably and my blood pressure was elevated and rising. An ambulance was called to take me to the ER, but I was released after several hours with no apparent damage. The experience caused me to re-evaluate my personal risk-benefit analysis. I concluded the benefits still outweighed the risks and decided to continue in the program. After a few more treatments, the director of the study called me with the information that my amyloids had completely cleared. I'm very pleased with the result and would ask this committee to recommend approval of the drug. Thank you for your time.

DR. MONTINE: Thank you.

Speaker number 7, please unmute and turn on your webcam. Will speaker number 7 begin and introduce yourself? Please state your name and any organization you are representing for the record. You have three minutes.

MR. VRADENBURG: My name is George

Vradenburg, Executive Chairman and Co-Founder of UsAgainstAlzheimer's. My organization is a national non-profit that receives programmatic support from Lilly, as well as thousands of other donors. I have no personal financial disclosures. I'm driven to my advocacy because three generations of my family have been touched by this damn disease.

At the risk of stating the obvious, Alzheimer's is a devastating, progressive, and ultimately fatal disease, and represents an unmet medical need of historic proportions. Treatments that slow this relentless trajectory at its early stage, before people lose their independence, are highly valued, as that slowing means more time with families, with friends, with life, and more time being alive to even more powerful medicines in the future.

The consistent evidence across different clinical measures in the donanemab trials demonstrate that this medicine delays functional decline, which we know from our own peer-reviewed

published studies is what patients want and find meaningful. Additionally, having a second disease-modifying therapy for patients and their doctors to consider will, in my view, dramatically accelerate the comprehensive health system adjustments patients so badly need to create a world where Alzheimer's is a treatable disease and not an inevitable fatal consequence of aging.

I understand that an issue before this committee is whether there should be limitations on access to this amyloid lowering product based upon the presence or levels of tau. While you appropriately will deliver your best scientific advice on this question, I urge you to consider the severe practical restrictions on patient access to this drug such, should such limitations be imposed, given the paucity of available tau PET scans in most of the country.

As has been noted today, there was inadequate representation in these trials of minoritized rural and low resource populations. This is not a unique issue with donanemab, but the

patient community and the field more generally must -- in my view, will -- tackle this issue with intentionality. The committee should act with clarity and urgency on this massive unmet need with confidence that people living with Alzheimer's will find a delay in progression shown by this drug to be meaningful and important in their lives, and patients and their families, informed by their physicians regarding the benefits and risks of donanemab, should be permitted the autonomy and personal agency to make the choices best suited to their individual preferences and needs in deciding to use this important new medicine. Thank you for your time today, and thank you for your service.

DR. MONTINE: Thank you.

Speaker number 8, please unmute and turn on your webcam. Will speaker number 8 begin and introduce yourself? Please state your name and any organization you are representing for the record. You have three minutes.

MS. BUTLER: Good afternoon. I'm Judy Butler from PharmedOut, a project at Georgetown

University that promotes rational prescribing and exposes unethical marketing practices. I have no conflicts of interest. Donanemab is the third anti-amyloid treatment for Alzheimer's disease to be submitted for FDA approval. Just like its predecessors, aducanumab and lecanemab, it does not improve how a patient feels, functions, or survives, and the net effect of these drugs appears to be harm. Three people in the donanemab trial died from brain swelling and/or bleeding, and more than one out of every three patients experienced at least one such episode, nearly double the rate for lecanemab.

Although it's unusual for adverse event effects to be renamed to hide their severity, that's what happened with brain edema and hemorrhage. They're now hidden behind the benign acronym ARIA. ARIA stands for amyloid-related imaging abnormalities, which sounds like a problem with the imaging tests; however, 2 patients who entered the lecanemab trial with mild Alzheimer's dropped 9 to 12 points on a 30-point memory scale

within a year of an MRI with ARIAs. That shows real harm.

The fact that adverse events were common in clinical trials of anti-amyloid drugs should be a flashing neon warning light. Remember, clinical trials enroll the healthiest patients possible. In practice, these drugs will be used in vulnerable elders who may have comorbidities and may be on multiple drugs. Adverse drug effects could be missed because brain harm symptoms include confusion and reduced cognition and could be mistaken for disease progression. Besides short-term harm, long-term harm is likely. Patients treated with anti-amyloid drugs lose brain volume faster than placebo, and brain shrinkage can be expected to worsen cognition.

The risks of these serious side effects outweigh any claimed benefits. The small statistical difference in rates of decline between treatment and placebo are not clinically meaningful. Patients and their families won't notice any change. The lack of individual data is

concerning. We don't know the difference between patients with MCI or mild Alzheimer's. We don't know the difference between patients with ARIA and those without. You've heard the sponsor say the ultimate goal is to treat people with no cognitive impairments. Early treatment of asymptomatic Alzheimer's is an industry concept that will necessarily treat many normal people who would never develop symptoms and can only experience harm.

In 2020, this committee resoundingly rejected aducanumab. That was the right decision; yet, under pressure from conflicted advocacy groups, FDA disregarded this committee's advice and issued an accelerated approval for aducanumab. It is the responsibility of this committee to advise the FDA not to approve donanemab.

DR. MONTINE: Thank you, speaker.

MS. BUTLER: Thank you.

DR. MONTINE: Speaker number 9, please unmute and turn on your webcam. Will speaker number 9 begin and introduce yourself? Please

state your name and any organization you are representing for the record? You have three minutes.

DR. PAPKA: My name is Dr. Michelle Papka. I have been doing Alzheimer's research for nearly 35 years and have been the PI on four recent trials of donanemab. These are my personal professional opinions, and I am not being compensated for my time.

When I work with patients, and I include loved ones in that word, I want them to be empowered to make informed decisions particular to their own personal situation and priorities. I advise them to consider all risks. Of course, all medications have potential risks, but so does having Alzheimer's disease and not getting treatment. We know decline is inevitable.

There is no perfect solution for a person with underlying Alzheimer's disease. Their best scenario involves choices and a personalized risk-benefit analysis. The benefit of a clinical trial or a potentially disease-modifying medication

is hope and the possibility of self-preservation for which I have seen many opt to take on considerable risks. Donanemab offers the potential to slow down the progression of disease both biologically and cognitively. It gives patients some control over moderating the course of a disease that they otherwise feel has taken control of them. For many, the possibility of maintaining abilities for a longer period of time is worth everything, including the risk of ARIA, and with respect to ARIA, I will add that we have managed patients well and safely through ARIA events, which occur in placebo groups as well.

Donanemab's unique approach of treating to clearance is, in my opinion, a major advantage. Why continue a medication when its target has been removed? Because of this design, I have been able to tell patients that their amyloid plaques have been cleared, including just this morning. It gets me teary every time and has been the highlight of my career.

Despite the seeming miracle of removing

plaques, donanemab is not a miracle cure. It does not stop cognitive decline, but it could be part of an effective cocktail, and we've got to start somewhere. I believe the question of whether or if the drug should be approved should be shifted to how and to whom it should be administered.

The healthcare system is not ready, nor is the health ecosystem. Let's focus our attention on that. For some patients, donanemab is a better option than what is currently available. We need to work towards personalized options delivered safely, and we know this drug is safe when patients are selected and monitored appropriately. For these reasons, I encourage this committee to recommend its approval. Thank you for your time and your service.

DR. MONTINE: Thank you, speaker.

Speaker number 10, please unmute and turn on your webcam. Will speaker number 10 begin and introduce yourself? Please state your name and any organization you are 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 member and allied organizations, along with university-based researchers around the world. We work to improve quality of life for people facing Alzheimer's disease and related disorders while advancing science and dementia.

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. You've received the LEAD Coalition's formal public comment letter, which was resubmitted to the FDA last Friday with an updated list of 265 signatories.

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

of clinical meaningfulness. For us, donanemab's 37 percent lower risk of progressing to the next clinical stage and nearly 5 and a half months, on average, slowing cognitive and functional decline are clinically meaningful. It gives us more time when that time is most precious; more time when that time contributes most to quality of life; more time for the next generation of improved therapies to become available and bless us with even more time in this early stage.

We understand that first-generation treatments are not cures and are not risk free. For our community, the balance of benefit and risk is reasonable in conjunction with recommended monitoring and management of potential side effects. While additional postmarket research on populations at higher symptomatic ARIA risk is warranted, for the majority of individuals, symptomatic ARIA risk is low, and decisions on the appropriateness of treatment with donanemab can be made by individuals in consultation with their physicians.

Our community values a treatment that significantly slows decline in cognition and function, particularly in activities of daily living, a treatment that meaningfully preserves the independence, dignity, and autonomy that we hold so dear. Today, you will help determine whether our hopes and our urgent unmet 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. MONTINE: Thank you, speaker.

Speaker number 11, please unmute and turn on your webcam. Will speaker number 11 begin and introduce yourself? Please state your name and any organization you are representing for the record. You have three minutes.

MS. CARLINO: My name is Sandra Carlino. My husband, George Carlino, was diagnosed with Alzheimer's disease in May of 2019. I have no conflicts of interest in this drug and I've received no compensation from Eli Lilly

Pharmaceuticals.

Our experience in this trial has been life-changing. We understand that his disease may never be cured, but the progression has slowed down immensely, to the point that to a casual observer or acquaintance, they would not know he has this condition. George's diagnosis at a young age reminded me of my father. My father was diagnosed with Alzheimer's disease at approximately 60 years old, and he died within five years. It was a terrible thing to witness and to go through.

Because of my father's experience, I was prepared for what most likely would follow George's Alzheimer's diagnosis and make comparisons over the course of this treatment with my father's journey. To my great surprise and relief, since being on this drug, George has not gone down the same path as my father. It's a night-and-day difference between the time George was diagnosed and where he is today, five years later.

When George began this trial, he went through the typical sundowning, mood swings,

unpredictable behavior, confusion, and overall depression. He went from having sundown episodes daily in varying degrees to having sundowning episodes every 6 weeks to 2 months. George now communicates with me and anyone else around him when he begins to feel he's going down the dark hole. Physically and mentally, George prepares himself to fight it, and he does. Rather than being non-communicative when these episodes begin, he will narrate and manage the occurrence, and even remember what steps he must take to effectively combat the negative emotions.

Through the course of this therapy, George has done great. A non-symptomatic brain bleed was found during a routine scan. As a result, his infusion was postponed for a month, and after follow-up scans, he was able to restart infusions and had no further complications. The benefits of this therapy far outweigh any adverse event, including the non-symptomatic incident that George experience.

We know this drug is not a cure. It is

preventing the progression of disease. George's ability to converse, keep up with the times, and remember things for more than a few hours is astounding. This drug has allowed us to live as normal a life as possible within the boundaries of Alzheimer's disease. We're extremely grateful to be part of Eli Lilly's TRAILBLAZER study. Thank you.

DR. MONTINE: Thank you, speaker.

Speaker 12 has yet to connect, so we're going to return to speaker 12. We're moving on now to speaker 13.

Speaker 13, please unmute and turn on your webcam. Will speaker number 13 begin and introduce yourself? Please state your name and any organization you are representing for the record. You have three minutes.

MR. SCHMIDT: I'm Jim Schmidt. I'm the steady partner and caregiver for my wife, Denise, who is a patient in the donanemab study at a site not far from our house. I have no conflicts of interest and I'm not being paid. We've been

married for 48 years. We started to see a slight decline in memory approximately three years ago. I came across an announcement in the local newspaper about available memory screening approximately a year and a half ago. Denise met the study entry criteria and was the last patient enrolled at the site. We felt extremely fortunate and we saw very few alternatives. We felt like we were doing something to help fight the disease.

I am retired after a 42-year career in the pharmaceutical industry. Twelve of those years involved design, placement, and monitoring of clinical trials for a major pharmaceutical company. It's interesting to experience a clinical trial from the other side. I am comfortable having Denise participate in this study, as regular MRIs check the safety. Based on my experience and having visited many sites in the past, I feel that our site is topnotch. Everyone at the facility is experienced, caring, and the communication is excellent. We've just completed visit 17, and so far, the drug has been well tolerated, no adverse

effects.

As a partner, I'm learning what it takes to be a good one. Naturally, my life has changed and continues to change. Denise was very involved in the everyday running of the household. I have had to take on new duties such as bill paying -- we never had any late fees before I started doing it --

(Laughter.)

MR. SCHMIDT: -- social calendars, et cetera. Most importantly, a good partner must respect the feelings of the Alzheimer's patient; avoid saying, "I just told you that." Just try repeating it patiently as many times as it takes; become a friendly reminderer; keep busy with stimulating projects and events such as shows, ball games, as inactivity seems to increase confusion.

We go to the gym, as exercise is essential, and lots of yard work to do this time of year as well. A healthy diet is also essential. We continue to socialize with friends and family. We also have four young grandchildren who we spend

time with. Jigsaw puzzles and crosswords are also good activities. To sum it up, having patience is a must. I always keep in mind, no matter how hard it is for me, it's much harder for Denise. Thanks for letting me speak.

DR. MONTINE: Thank you.

Speaker number 14, please unmute and turn on your webcam. Will speaker number 14 begin and introduce yourself? Please state your name and any organization you are representing for the record. You have three minutes.

MS. RIGBY: My name is Kathy Rigby. I am not being paid or compensated in any way to give you this message today. My husband Brent has stock in many companies, Eli Lilly being one of them, that being a very small amount of shares. With that being said, thank you for this great opportunity to speak to you today.

Six years ago, my husband's sister-in-law, Angela, died from Alzheimer's. She was a wonderful person. Brent's brother said he would have paid any amount of money to save his dear wife. We have

become quite sensitive to this disease. In 2023, I was diagnosed with Alzheimer's. It was like a slap in the face, along with a punch in the gut. All that I can say is that I was blessed to have great doctors that led me to Charter Research, where I received the medication donanemab. I need to give Charter Research such great thanks for helping me through the process, as well as educating me along the way. I love them.

I am indeed a success story. I was told that there may be complications with donanemab, possible brain bleeds. I had none. I never had one single ill effect from this medication. I know I can't be the only one. Recently, my husband and I wondered how we might help get this medication approved for use for other Alzheimer's patients as soon as possible, and then I was grateful to be given this opportunity to speak to you today.

My symptoms were stuttering. I could not get some words from my brain to my mouth. The next one, I became anxious to the point of tears, constant fear, and then if I was interrupted by

anything, I could not come back to that thought; it was gone, like it was literally sucked out of my head. Now, after having had finished 6 months of infusions, I am different, I am better, I have not been stuttering. My anxiety has greatly diminished. I can now be interrupted and usually come back to that thought. It is so much better. I have gotten so much better.

I am so glad that I have been given this chance to live, to live a life of purpose, and now possibly help others to be so blessed as I have been. I would assume any medication has its negatives, but I think the positives of donanemab far outweigh any negatives, especially after watching my husband's sister-in-law suffer for 6 years with Alzheimer's and die at the age of 63.

The plaque has been removed from my brain, but I realize the cause is still there and that the plaque could return. And if and when it returns, I would be grateful to have access to this great medication. I now have a chance to continue to live my life in a way that I am still Kathy Rigby,

and that I know who I am.

DR. MONTINE: Please excuse me, speaker.

MS. RIGBY: Thank you so much. Thank you.

DR. MONTINE: Thank you. Please excuse me.

Speaker number 15, please unmute and turn on your webcam. Will speaker number 15 begin and introduce yourself? Please state your name and any organization you are representing for the record. You have three minutes.

DR. SCHREIBER: I'm Dr. Curtis Schreiber, neurologist and dementia specialist in Bolivar, Missouri. I'm in a full-time practice as a general neurologist and Medical Director of Missouri Memory Center at Citizens of Memorial Healthcare in Bollaram, Missouri. I'm speaking for our center and for our patients.

This is a rural practice which is part of a small but thriving healthcare system that serves nine counties in southwest Missouri. This is my 33rd year of post-residency practice. I've been seeing Alzheimer's patients since day one, and I saw a bunch this morning. This in the trenches

experience that I've had with my patients is what I want to share with you today.

First, my disclosures; I've been the clinical trial PI at our center for Lilly AD clinical trials and I've participated with Lilly as an advisor and speaker bureau member, and not only Lilly, but several other pharma companies in the Alzheimer's disease space as well. In research studies, I have experience with solanezumab; gantenerumab, and remternetug. In the clinic, I prescribed aducanumab and lecanemab. ARIA occurs in these settings, and I've found this to be a manageable concern.

For today's meeting, I want to highlight my experience with donanemab. I am the PI at our site for the TRAILBLAZER-ALZ2 study. At our center, it is our clinic patients who become research subjects, so we know them well. As it turns out, the majority of subjects at our site for the TRAILBLAZER-ALZ2 study were part of the open-label safety addendum. I saw my own patients on donanemab having results that demonstrate the

real-life clinical meaning of this type of treatment.

For example, in the middle of the study, one subject's spouse, an important study partner, developed a serious medical problem that required a solid organ transplant. The patient, who had gradually become more dependent on the spouse, was able to step up as the caregiver and managed all the many issues around the transplant. Another patient, who had retired from work as a building contractor due to cognitive decline, came for a routine clinic visit towards the end of the study and reported that he had gone back to work part-time and was managing well.

These patients' experiences illustrate the types of outcomes that make a difference for them but may not be captured in the standardized study outcome measures. Just like my patient who's a contractor, building a medical practice is much like building a house. The science and the clinical trials make a firm foundation.

The data you have to review strongly

supports the approval of donanemab. Once the scientific foundation is laid, the house of treatment is built and the pinnacle can be reached, not just by the science of medicine, but also by the art of medicine, where clinicians can use the tools they are given to the best advantage of each patient.

The key to ultimate success is individual, as no two Alzheimer's patients are exactly the same. The pinnacle of success for Alzheimer's treatment is the right patient, at the right stage, with the right drug, that best suits that patient's individual circumstances. We need more tools in this fight against Alzheimer's disease. Approve donanemab. Thank you.

DR. MONTINE: Thank you.

Speaker 16, please unmute and turn on your webcam. Will speaker number 16 please begin and introduce yourself? State your name and any organization you are representing for the record. You have three minutes.

DR. SABBAGH: Thank you, Chairperson. My

name is Marwan Noel Sabbagh. I am a cognitive behavioral neurologist at a major medical institution in the southwestern United States. I will not be representing my institution or healthcare system with my remarks. All of my comments are my own as an individual neurologist, and as an AD thought leader, I bring perspectives as the prescribing neurologist that treats patients.

I have no proprietary interest in the molecule or the company. I've not advised Lilly on donanemab, although I've advised Lilly in the development of other drugs such as solanezumab. I have no vested interest in the outcome of this discussion. I have not been an investigator in the phase 3 TRAILBLAZER-ALZ2 trial; furthermore, I do advise many companies developing drugs for Alzheimer's disease.

Why am I here? I'm here because I am pro treatment. Until recently, there have been no successful disease-modifying therapies. Monoclonal antibodies have been in development for almost

20 years. The filing of donanemab is the third we have seen with directional concordance of lowering of amyloid and slowing of cognitive decline. Donanemab may indeed bend the curve. I have many patients waiting for this treatment option. Despite the broad opinions, patients understand that AD is a unidirectional fatal disease. I spend hours every week conveying this information, and it is heartbreaking. We cannot rely on hope and optimism. Patients want solutions, and I have that conversation a lot.

Let me give you an example. I saw a patient last Thursday. He is a CEO of a company. He's 82, and he has 10,000 employees. He repeated himself 4 times during his visit with me. He knows there's something wrong. He is terrified. His plasma biomarkers show that he actually has elevations in p-tau and lowering of amyloid. I actually, while I was waiting to speak today, saw his amyloid PET. It is positive. I'm going to see him tomorrow to disclose to him that he has Alzheimer's pathology in his brain. He knows there's something wrong,

his wife knows there's something wrong, and they would do anything to change the outcome.

The reality is that we know people who have mild cognitive impairment and the risk factors for progression. We know that amyloid presence, APOE genotype status, neuropsychological testing, and low hippocampal volumes predict progression. I've been an investigator for bapineuzumab, solanezumab, crenezumab, gantenerumab, and aducanumab. I've seen patients, real patients, on long-term monoclonal antibodies that did not get worse.

When we consider the risk-benefit analysis, we need to be realistic as we counterbalance the fact that patients have 100 percent probability of getting worse and losing autonomy juxtaposed against 6 percent chance of symptomatic ARIA. We go to great length to mitigate the risk. We select patients who have the best outcomes. Although I am not a donanemab investigator, I have seen the publicly available dona data, data that --

DR. MONTINE: Speaker? Thank you, speaker. Thank you so much for your comments.

We will move on to speaker 17. Please unmute and turn on your webcam. Will speaker number 17 begin and introduce yourself? Please state your name and any organization you are 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. While the Alliance receives funding from the sponsor and competitors, we don't endorse any therapy or take positions on FDA approval of specific medical products. In fact, the Alliance strongly believes that the FDA safety and effectiveness standards have remained steadfast.

The FDA has consistently based its decisions on sound science in support of its true public health mission. No other agency even comes close to having the FDA's biomedical expertise. When it comes to evaluation of risk-benefit for people living with early Alzheimer's, the FDA senior career staff have acted with integrity and decision

making and carefully guarded their independence in a highly politicized environment.

The adverse events related to donanemab are very low, and especially when compared to almost any oncology drug, yet because Alzheimer's is a deadly disease primarily affecting older adults, clinical paternalism is common, and we unfortunately heard that paternalism clearly today from the non-expert at PharmedOut. We've also heard senior officials in the Medicare program recklessly refer to people living with early Alzheimer's as, quote/un quote, "relatively healthy." I wonder, would they say the same about someone living with a small malignant tumor?

Donanemab is part of the first wave of disease-modifying monoclonal antibody therapies for early Alzheimer's. There's only one FDA-approved first-line therapeutic in this class currently available, but availability is highly rationed in Medicare and in the private payer market. If the evidence and FDA recommendations support approval, it would be a blessing for families to have a

potential second treatment option.

The community understands that donanemab is not curative but has shown promise in clinical trials in delaying progression of disease. This is a key importance to people living with early Alzheimer's, where quality-of-life outcomes, such as cognition, personality, and the ability to care for oneself, are the ones that matter most. We encourage everyone here to recognize that people living with early Alzheimer's and their families are more than capable of assessing risk-benefit with their clinicians and to mutually decide the right treatment decision for them.

On a personal note, my aunt is 62 years old and living with early disease. She went through evaluation for Leqembi but did not qualify due to microhemorrhages. My 83-year-old mom is further along, and I care for her every weekend. These women are my heart. Neither of them will qualify for this drug. I'm here on the Alliance's behalf and on their behalf to say, it's crucial that we get this right.

Unfortunately, the public's trust in science and government has seen better days. How we express ourselves, both in agreement and disagreement, shapes narratives and can contribute to misinformation. To the advisory committee, please consider how your dialogue today will help or harm the public's trust in science and the FDA. Please serve as true, constructive advisors to the FDA's impartial, rigorous, and expert review. Thank you.

DR. MONTINE: Thank you.

Speaker 18, please unmute and turn on your webcam. Will speaker number 18 begin and introduce yourself? Please state your name and any organization you are representing for the record. You have three minutes.

MR. DWYER: My name is John Dwyer. I'm the President of the Global Alzheimer's Platform Foundation, a not-for-profit enterprise dedicated to speeding the conduct of Alzheimer's and other neuroscience clinical trials, making them more effective for all potential patients. My own

father died of Alzheimer's disease; his mother died of Alzheimer's disease; six of his eleven siblings died of Alzheimer's disease, so this also a very personal matter.

We have been part of every disease-modifying therapy dealing with subjects in the MCI mild AD category. We have helped with the recruitment and retention of volunteers in these studies and seeing both the compounds that have not succeeded meeting their endpoints and those that have. We were in the TRAILBLAZER studies, and I will say that we saw in that study, the way Lilly conducted it, one of the best studies conducted in the field since 2019.

As a consequence, taking the totality of the data and the very real threat to patients that have been previously described, the global Alzheimer's platform seeks the approval of this compound and to make its availability to the public and distribution as easy and accessible as possible. It is in that respect I do want to speak to one of the issues that Dr. Krudys [indiscernible - 5:52:53] raised, which is we are very active in the

biomarker area, and with the way the cutoffs worked in TRAILBLAZER, it's clear that that had a lot to do, despite Lilly's concerted efforts, to get folks from the African American community and the Latino community enrolled in the study. A lot of people were screen failed because they had less than the required amount of beta amyloid plaque.

Our own studies show that many subgroups provide clinicians with a much lower level of beta amyloid plaque even though they describe and have the clinical evidence of MCI or mild AD, and in that regard, we encourage the committee, the FDA, and Lilly to take it upon itself to really ask how are we going to communicate to these communities how to evaluate patients, what is true amyloidosis consistent with Alzheimer's disease, so this drug and its class can be made available to these groups that are not being well represented in trials.

DR. MONTINE: Thank you, speaker. We need to move on to the next speaker.

MR. DWYER: Thank you very much.

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

We'll move to speaker 19. Please unmute and turn on your webcam. Will speaker number 19 begin and introduce yourself? Please state your name and any organization you are representing for the record. You have three minutes.

MS. GARCIA: Good afternoon. My name is Myra Solano Garcia. I live in Upland, California, and I am a donanemab patient. I don't have any financial ties to Lilly or other pharmaceutical companies, and I'm not being compensated for my time.

I'm 65 years old, and I was diagnosed with Alzheimer's three years ago. I am now in a clinical trial through USC, but what I wanted to tell you is that this disease is running in my family. My mother's two sisters had the disease. One aunt got all of the care that she needed while my other aunt, who was a widow with a special needs child, my cousin, lost her condo and was left out on the ground, and that was a really, really sad day for our family. As I mentioned, Alzheimer's has been in the back of my mind ever since that

time.

I was a college vice president, but I lost my vice presidency during COVID. I continued to seek work, but that was evading me. I was hired by the San Diego Symphony Orchestra as a vice president, and that only lasted for three months. I did the same work at another organization, and it was the same problem, and through that time, I knew what was going on with my cognition. I was in a clinical trial through USC, and a neuropsychiatrist was the one who was able to diagnose me.

So what I want to leave with you -- and, of course, all of this was happening during COVID, so that was a terribly difficult time. But the disease was taking everything away, everything that I had hoped for over time. I won't remember who my husband is going to be -- or who my children are, but donanemab has been very, very helpful to me. I have been on the clinical trial for about 2 to 3 years, and I can tell you that I have had not a single bit of problem with it.

DR. MONTINE: Excuse me, speaker.

MS. GARCIA: Yes?

DR. MONTINE: Please forgive me for interrupting. Your time has expired. Would you please finish your comments?

MS. GARCIA: Yes. At this point in time, I'm in a plateau, and I'm very happy about this. And I hope that because of my experience with donanemab, I strongly encourage the FDA to continue this drug and to make it available to people like me. Thank you so much.

DR. MONTINE: Thank you.

Speaker number 20, please unmute and turn on your webcam. Will speaker number 20 begin and introduce yourself? Please state your name and any organization you are representing for the record. You have three minutes.

MR. PHILLIPS: My name is Thomas Phillips. I'm representing myself. I'm not being compensated and I have no conflict of interest. I want to thank you for the opportunity to speak today.

As an individual living with mild cognitive impairment, I am grateful for the Food and Drug

Administration's, and this committee's, diligence in evaluating the safety and efficacy of this much needed treatment. While I understand and appreciate your duty to ensure that the treatment before you, and those like it, are safe and effective, I also ask you to balance those considerations with the clock that is ticking in front of me, my family, and all those living in the early stages of Alzheimer's disease.

When I received my diagnosis, my wife and I experienced shock and grief, as so many do. When we asked what can we do in the face of a progressive, fatal disease, I can exercise, I can read and otherwise exercise my mind, and I can socialize, but the bottom line is that while those are good things to do, regardless of someone's circumstances, they do not slow my cognitive impairment. They do not delay what is to come.

So in the space of a few short months, my wife sold her business, dropped everything, and moved up our climb line of what we had always planned to do well in the future. We moved to

Denver to be close to family, including two of our five grandchildren, who I want to babysit for as long as possible. With an 18 month old to a 14 year old, and everyone in between, buying presents for the grandchildren takes a long time, and I want to keep buying presents.

One of the other reasons we moved to Denver was to be closer to the great outdoors where we can hike and take road trips through the mountains. It is not lost on me that someday I won't be able to do those things on my own. I won't be able to cook a meal without being watched for safety sake. And while I am grateful to have the support of a family who will care for me, the very idea that I might be able to cook meals or hike with my wife for even just a few more months is worth fighting for.

And more time isn't just for me. My wife has been my strength since my diagnosis, but she knows what will come. A delay in my progression for her means more time to plan for that inevitable future. That opportunity provides its own form of comfort. We want that time and that hope. I want

to run at those things that give me that chance at more time, and I thank you for considering my perspective.

DR. MONTINE: Thank you.

Speaker number 21, please unmute and turn on your webcam. Will speaker number 21 begin and introduce yourself? Please state your name and any organization you are representing for the record. You have three minutes.

MS. GATES: Good afternoon. My name is Maria Gates, and I am not being compensated for my testimony. Five years ago, my husband George was diagnosed with early onset Alzheimer's at age 57. Early onset Alzheimer's robs Americans productive decades. Today, George is 62 and dealing with an illness for the past five years that is thought to affect only the very old. George was strong, healthy, and athletic. Suddenly, he couldn't remember how to do his job. Little by little, his freedom is being stolen by dementia.

George has participated in the TRAILBLAZER-2 clinical trial for donanemab for the past three

years, receiving 38 of 40 monthly infusions. He has experienced no side effects or issues with this drug, but has experienced positive physical and cognitive changes; whereas he moved slowly, he now walks with normal strides and shows strong posture and gait. His chronic sensitivity to cold has ceased. He became more talkative, follows conversations, and watches TV with interest, and made it funny commentary. He now stretches out his hand to shake hands and addresses people again.

Recently, his urologist commented on a noticeable change in his personality. I attribute these improvements to donanemab, as these benefits began approximately 8 months ago. His activities of daily living have improved. He is showering on his own, his oral care is on his own, as well as dressing. I am so proud of the progress and sacrifice that George has made, and we both feel so lucky that he received donanemab. I feel distress for anyone who may be denied this drug.

What is the benefit of donanemab? The benefit for George, myself, our family, and our

community is increased time and quality of life for those suffering from this terminal illness. For example, George will walk his youngest daughter down the aisle in August and welcomes a new granddaughter in October. It's been five years since his diagnosis. He's clearly benefited from this drug. At minimum, he's plateauing.

Another benefit is decreased caregiver stress and increased time for caregivers to rest or earn an income, also increased time that patients can remain at home versus a costly facility. What is the risk of not having donanemab? One hundred percent catastrophic incapacitation leading to death is the certain outcome.

This drug needs to be provided early upon confirmed diagnosis to help stave off the inevitable grip of Alzheimer's. America needs to recognize the economic devastation of Alzheimer's. Every American is affected; everyone. Our family lost more than $3 million in lost wages because he became disabled 10 years too early. That is money that will never be taxed by the federal government,

New York State, Social Security, or Medicare taxes; instead, he had to request Social Security and Medicare benefits early. As I have clearly laid out, everyone loses. Let's make it a win for families. Please recommend approval of donanemab and ease everyone's burden. Thank you very much for your time.

DR. MONTINE: Thank you.

We're returning to speaker 12. Speaker 12, please unmute and turn on your webcam. Will speaker number 12 begin and introduce yourself? Please state your name and any organization you are representing for the record. You have three minutes.

MR. TAYLOR: Good afternoon. My name is Jim Taylor. I lead Voices of Alzheimer's, an advocacy organization for people living with Alzheimer's disease and their care partners. My wonderful wife Geri was diagnosed with AD in 2012. I am here to represent the voices of millions of Americans living with Alzheimer's. I am also an FDA appointed patient advocate and have served at prior

Alzheimer's adcoms. I thank you for the work you did to prepare for today and for your service.

I urge you to consider the perspective of millions of Americans living with Alzheimer's, their families, and their care partners, to make a positive recommendation in favor of donanemab approval. The development of safe and effective treatment to prevent, delay, slow, and better manage Alzheimer's disease and related dementias is one of our most pressing public health challenges. Treatment options bring tremendous hope to affected families and offer priceless additional time for early-stage patients.

Geri and I speak from personal experience. For a number of years, Geri participated in a clinical trial for a now approved mab treatment. We have experienced the benefit of additional years in the mild stage of the disease when we could continue to live our lives and our advocacy in high gear.

The FDA has repeatedly delayed donanemab's approval. For patients, there is no time to wait.

Donanemab must be approved as soon as possible. Research estimates that every day, more than 2,000 individuals transition from the early to the mild stage of the disease and are, therefore, no longer eligible for this treatment. We know donanemab is not a cure, but it will give patients and their clinicians a crucial second treatment option to slow progression. We are entitled to that choice.

We also understand that like most drugs, there are risks associated with this treatment, some of which are serious. Still, the decision of whether to take these risks should be made by the patients, their physicians, and their families. When you make your recommendation today, I urge you to remember that people in the early stage of Alzheimer's are facing years of an illness that will progressively rob them of themselves, their independence, their ability to function.

Like all of us, we want a choice regarding our treatment. We want options of treatments that can delay the onset of the worst symptoms of this

disease. We want time with our families to do the things we love, to live life on our own terms as long as we possibly can. I urge this advisory committee to make a positive recommendation today in favor of donanemab approval. Thank you.

DR. MONTINE: Thank you, speaker.

The open public hearing portion of this meeting is now concluded and we will no longer take comments from the audience.

We'll take an approximate 12-minute break. Panel members, please remember that there should be no discussion of the meeting topics with other panel members during the break. We'll resume at 2:50. Thank you.

(Whereupon, at 2:38 p.m., a recess was taken, and meeting resumed at 2:50 p.m.)

Questions to the Committee and Discussion

DR. MONTINE: Welcome back.

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 will 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 have read each question, we will pause for any questions or comments concerning its wording.

Question number 1 is a discussion point. Discuss whether the available data provide evidence of effectiveness of donanemab for the treatment of Alzheimer's disease, AD. Additionally, discuss the support for effectiveness across tau positron emission tomography, PET, subgroups, including the no/very low tau population that was excluded from the placebo-controlled trials.

Are there any questions about the wording of this discussion point?

(No response.)

DR. MONTINE: If there are no questions or comments concerning the wording of the question point, we will now open the question to discussion. To the panel members, please, if you wish to add

your comments or discuss the evidence concerning effectiveness, and especially the point of the effectiveness across the different tau PET subgroups.

Yes, please?

DR. PRESS: Yes. I'm happy to go first. For me, the high tau subgroup is of a little bit more concern than the no/very low. I understand that the no and very low people were excluded from the trial but, by definition, they had to have mild cognitive impairment. And all the evidence so far, both from donanemab and from other medicines in this category, is that treating earlier is more effective. So it's pretty strong a priori evidence that there's not going to suddenly be a loss of efficacy at some arbitrary tau cutoff at the low end.

Having said that, the converse is also true that there's less and less evidence for efficacy at high tau levels, and that I think poses a bigger challenge. It poses a bigger challenge in the clinic for when we should stop therapies because we

have people who are continuing the therapies, and we don't know when amyloid reduction is no longer going to be beneficial, and I think that's a challenge. Having said that, there's certainly evidence, some evidence, for some efficacy, even at high tau levels, but to me, that was the bigger concern.

DR. MONTINE: Please, Tanya.

DR. SIMUNI: Tanya Simuni. I believe that based on the data provided by the sponsor and summarized by the sponsor, summarized by FDA, the study met its prespecified primary and key secondary endpoints, and based on that, the conclusion should be that the therapeutic isn't effective in the target population.

Then the next sentence of the question, can we extrapolate from that conclusion that the therapeutic is to be clinically effective in the population with no/very low tau because that population was not included in the randomized placebo-controlled study? We don't have the data; right? We do have the data on the target

engagement, so we need to extrapolate, and at that point, the data on the target engagement, the curves are very consistent with the population studied.

Then we need to ask the question, or at least I'm asking myself the question, is it feasible, practical, to require PET tau imaging in the population? Based on the data presented, about 8 percent of the population in this stage 3-4 Alzheimer's disease will have no/very low tau. Is it practical, feasible, and indicated to require imaging for the population at large to further assess that population?

I personally don't think so. I think that the preclinical data is supportive. The whole cascade of the mechanism is supportive. The target engagement data is shown, and provided that the safety is not preclusive -- and we didn't hear such -- I would support the indication as stated across the continuum of tau PET imaging without requirement for additional PET tau imaging. So that's my summary.

DR. MONTINE: Thank you. I'll add, the peripheral biomarkers were also supportive.

Merit, you were next.

DR. CUDKOWICZ: Yes. I don't have too much to add. I also agree that phase 3 as well as the phase 2 provide robust evidence of effectiveness, and the phase 3 hitting on the primary and the key secondaries, so that is all good. I think for the no or the very low, all we have is really the biomarker effect and the safety from the extension study, but there's precedent from other studies that lowering amyloid is associated with clinical effect as well.

I wanted to touch on the high tau, and I'm not the Alzheimer's expert. It is true, at least on the graph from the FDA, the high tau group didn't hit on the primary, but it did on the CDR-SB. And I actually don't know whether that's driven by the variability in that group or the more aggressive group, but I think the goal is to try to treat early, and it would be perhaps nice to leave this to the physician and the patient about the

decision of the risk-benefit in that group.

DR. MONTINE: Thank you, Merit.

Dean, you were next.

DR. FOLLMANN: Yes. Dean Follmann. Just to discuss this question, I thought the evidence was very strong in the trial showing the effectiveness of the drug. I particularly like the analysis that talked about the length of time extended for the decline and also how you delayed the clinical staging. I think those are meaningful to patients and providers, and I think if you do an analysis that looks at the delay in staging, it might be greater effect for the earlier stages as opposed to the later stages.

Regarding the no or very low tau question, I'm not so comfortable extending it to this group. If you look at the data, there's less evidence of a benefit, or weaker benefit, in those who have low tau in the trials, and then I don't know what happened with the no or very low tau subgroup. This was expected by the sponsor and the FDA, and it's one of the reasons for the enrichment design,

that you expected there'd be this longer time to achieve a benefit. So in my mind that suggests there could be a reduced benefit or I don't know if there will be one. Later, we'll talk about risk and benefit, so less in benefit means something different when you're evaluating risk compared to a larger benefit.

I think the enrichment design that you did made perfect sense as a strategy, where you want to place your bets on where you think you'll see the largest benefit, and then in the progression of evaluation of a drug, the next thing would be to do exactly what you're doing, which is to look at primary prevention.

So I think we'll be getting data about the effect of the drug in an earlier population, more broad population, so one possibility is wait for that or you could say we'll make a judgment that it's ok not to include testing for tau. I'm just wary of extrapolating to that. I don't know if there's a way to predict tau levels. I guess that wasn't very promising from what you said, so we

just have to either be wary or make an extrapolation, and I'm wary of that.

DR. MONTINE: Excuse me. I was taking notes.

Sarah, you were next.

MS. DOLAN: This is Sarah Dolan. I definitely need to have a little clarification here. My understanding from this discussion earlier and the presentations is that gathering tau, getting tau measured in the community, is not an easy thing to do; correct? So I think we really need to decide, if we move forward, if this drug gets approved, is that going to be required or not. And it really doesn't matter what -- I mean, we see the benefit across the range of tau burden, the benefit through the range of patients, tau burden there, so I think we need to first decide is there going to be a tau measurement needed or not, and I would vote for not because it has shown to be clinically a benefit across all stages there.

DR. MONTINE: Thank you, Sarah.

Kathleen, you were next.

DR. POSTON: Thank you. Kathleen Poston. I will directly address that issue and was the comment that I wanted to make. I share the concern of not having data in the low group, and I believe the enrichment strategy was a wise one because the percent change over time in that low tau group, based on observational data modeling, would have been very small, and the ability to detect a loss of change in a group that is progressing very slowly would have been difficult.

So while the the overall slowing presumably would have been much less over the short period of time of the trial, I am comfortable extrapolating because of the three different biomarkers that it did show engagement with, both the amyloid PET, the tau plasma, and the GFAP. Of note, tau plasma is not a pure tau biomarker; it is a mixed amyloid tau measure. So it's not a pure tau biomarker, but it did show that change.

Speaking to the practicality, this is a real concern. Tau PET is not the same thing as amyloid PET, and having amyloid positivity/negativity is a

fairly commonplace thing that somebody is able to do, whether it be in CSF or in PET, and soon likely in plasma as well. But the degree of tau abnormality can only be determined via tau PET, and it's not just a visual read that can be done. This requires very sophisticated, high tertiary center, academic centers that have imaging capabilities, in many cases, to be able to do.

So from a very practical perspective, I think this would be not a wise thing to have as a barrier. If there had been no biomarker data available in that low group, I would have much more pause, but with the biomarker data there, both in amyloid PET and in two plasma markers, I am comfortable with that, both from a data perspective and from a pragmatic perspective.

DR. MONTINE: Thank you.

Nilufer, please.

DR. ERTEKIN-TANER: Nilufer Ertekin-Taner. I agree with the comments, which indicated that we do not have clinical outcomes data and delay data on the no and very low tau population, and this

data needs to be collected, especially in light of what we know about amyloid-only type of patients, the so-called pathologic aging who may be deemed to be a more protected or resilient population, so this data needs to be collected. But the practical question is, should tau PET be stipulated? Should it be required?

From a practical standpoint, it is my impression that it should not be. Getting amyloid PET is already hard enough, and already these types of studies and inclusion in these types of trials are easier for patients of certain social ethnoracial groups and geographical location. Inclusion of requirement for PET tau will further limit the number of patients who can have access to these types of medications. So it's a nuanced situation where, on the one hand, we do need to have the additional data on the no and very low tau population, and on the other hand, we should not require having tau PET for access to these medications.

DR. MONTINE: Thank you.

Cindy?

DR. CARLSSON: Thank you. I agree with many of the comments that have been said. I think one additional point I wanted to make was, I know within the public comments and other reviews that people have raised, the point about these imperfect measures that we have for cognition and function, again, these are the standards of our field currently for function, cognition, and then seeing the change from stage. So it looks across all those endpoints, and it seems like there's good clinical efficacy in those who were included in the clinical trials in the randomized component. And I agree; I think the biomarker data really support that even in that no/very low tau population, there was some efficacy.

So while I know a lot of my colleagues in geriatrics worry about is this really clinically meaningful, I think that's something for our field to continue to work on. We see the participants and people's perspectives that were shared with us today, and trying to match those up with objective

data that we can measure in clinical trials is challenging, but I think the data that have been provided give us the best clinically meaningful data that we have to date.

Then for disparities and access, I think a few points that have been made in the public comments that were submitted online, people brought up points about underrepresented participants having access, and by approving this, at least, and having something that would have more focused endpoints, a shorter duration, monthly, actually could improve access to antibody therapy because of that availability. While at the same time, I think there's a continued huge need for us to improve our randomization and inclusion of persons from different backgrounds because I don't think we can really say this is effective in all people groups, which is still a whole issue with our clinical trials mechanism as a whole.

But I agree, helping to oversee a clinic network of 35 clinics across the state of Wisconsin who live in rural areas, urban areas, access to tau

PET scan would be virtually impossible for a lot of these communities. So I think that given the data that we have and the scientific knowledge that we have of how amyloid and tau progress, I would say we do not need tau PET in this population but just amyloid PET.

DR. MONTINE: Thank you.

Are there any other members of the panel who wish to comment?

Yes, Costantino?

DR. IADECOLA: So assuming that the cognitive benefit comes from reducing amyloid beta, and on the finding that the reduction of amyloid beta can be observed across all the tau groups, and in view of the improvement of the biomarkers shown, I think that getting the tau PET would be a barrier to restrict further the population that's going to get a benefit from this drug; still, it's going to be 10 percent or less of all the Alzheimer's patients. So my feeling is that the tau pet will not be required.

DR. MONTINE: Any other comments? Otherwise

I can briefly summarize.

(No response.)

DR. MONTINE: The two parts of the questions you very nicely put it, is there effectiveness for donanemab in the treatment of Alzheimer's disease, it sounds like the committee is in agreement that the data is there to support that. Then there's this one group which we don't have direct data; we have indirect data through biomarkers, which is supportive. There is some concern around extrapolating the trial results overall to this subset of no/low tau, but although there is legitimate concern to extrapolate beyond where we have direct data, at least the vast majority of the committee feels as though imposing a requirement for tau imaging is not necessary and would raise serious practical concerns and access concerns to the treatment.

Is that a fair summary? It's really meant to provoke someone who disagrees to keep the discussion going.

(Laughter.)

DR. MONTINE: Does anyone strongly disagree with what I said?

(No response.)

DR. MONTINE: May we move on to the next?

If there are no further questions or comments concerning the wording of the question, we'll now begin with the voting process. Please press the button on your microphone that corresponds to your vote. You will have approximately 20 seconds to vote. Please press the button firmly. After you have made your selection, the light may continue to flash. If you are unsure of your vote or you wish to change your vote, please press the corresponding button again before the vote is closed.

Question number 2 is a vote. Do the available data show that donanemab is effective for the treatment of Alzheimer's disease in the population enrolled in the clinical trials with mild cognitive impairment and mild dementia?

In determining your vote, if you believe there is efficacy across the entire population or

efficacy only in a subset of patients, e.g., those with low-to-medium and high tau, please indicate that with a yes vote. If your assessment is that efficacy is not established in any subset of patients, then please indicate that with a no vote. Explain the rationale for your vote. If you voted no, please indicate in the discussion of your vote what additional data would be needed to support the effectiveness of donanemab for the treatment of Alzheimer's disease.

I apologize if I did those two out of order. That's the vote, and then I had initially read the instructions on how to vote. See the panel in front of you and please vote either yes, or no, or abstain. They said it will take about 20 seconds, and then the voting will close.

(Voting.)

DR. SEO: This is Jessica Seo, DFO. The results are in. For the record, we have 11 yeses, 0 noes, and 0 abstentions.

Dr. Montine?

DR. MONTINE: Now that the vote is complete,

we will go around the table and have everyone who voted state their names and their vote, and if you want to, you can state the reason why you voted as you did into the record.

We'll start with Nilufer, and then just work our way around.

DR. ERTEKIN-TANER: I voted yes, and based on --

DR. MONTINE: Excuse me, Nilufer, for interrupting you. Just for the record, your name and your vote.

DR. ERTEKIN-TANER: Yes. Nilufer Ertekin-Taner. I voted yes based on the data and the value that the best interest of the patient is the only interest to be considered. I will describe my vote. It is with the knowledge that ε4 negatives and ε4 heterozygotes, there is efficacy and the risk is acceptable. The information is unclear or insufficient for ε4 homozygotes.

It is also with the understanding that we need more data in African Americans and Latin Americans, and that there isn't data on special

populations, including patients with Down syndrome and autosomal dominance Alzheimer's disease patients. It is everyone's duty to obtain that information going forward.

DR. MONTINE: Thank you.

Dean?

DR. FOLLMANN: Yes. Hi. My name is Dean Follmann. I voted yes. I thought the evidence over the population studies in the trial was very strong and consistent across subgroups.

DR. POSTON: Kathleen Poston. I voted yes. The clinical data across subgroups, as well as the biomarker data, was convincing of the effect. I agree with the concerns of lack of information in underrepresented groups, particularly the African American and the Hispanic. That will be important in the future to obtain to make sure that these encouraging findings can be extrapolated to everyone with Alzheimer's disease.

DR. MONTINE: My name is Thomas Montine. I voted yes for the reasons already given by my committee members.

MS. JOHNSTON: Colette Johnston. I voted yes. I feel like the risk is acceptable. I would like to see -- and I concur with you -- more data in the underrepresentative groups in this particular study.

MS. DOLAN: Sarah Dolan, and I voted yes. There's a huge unmet medical need here that hopefully can be addressed. And I do give a lot of credit to everyone's discussion here talking about the benefit of having unique individualized patient discussions and deciding everybody has their own unique risk-benefit assessment that they have to make, and that can even change throughout the course of a disease. So I believe that a lot of information, a lot of education, needs to be done with the prescribers and with the patients and their care partners and families to follow up and manage these patients.

DR. CUDKOWICZ: My name is Merit Cudkowicz. I voted yes because of the clinical biomarker efficacy across the entire population.

DR. SIMUNI: My name is Tanya Simuni. I

voted yes, and I think that I summarized my reasoning for the world in the discussion.

DR. PRESS: My name is Daniel Press, and I voted yes for the reasons already stated by my colleagues.

DR. IADECOLA: Costantino Iadecola. I voted yes for the reasons stated.

DR. CARLSSON: Cindy Carlsson. I voted yes because the standard field of Alzheimer's cognitive and clinical progression measures showed improvement with therapy, and I do not think the tau is necessary because it doesn't have any clear impact on scientific validity, safety, and would be a barrier access.

DR. MONTINE: Thank you.

We will now move on to question 3, a discussion question. Question 3, discuss the dosing regimen used in the clinical trials that completed treatment based on reduction of amyloid plaques on PET imaging, and if there are scientific and/or clinical considerations that may factor into a decision to stop or continue dosing with

donanemab if approved.

Tanya, please.

DR. SIMUNI: I guess I will start. From a scientific standpoint, I find the design of the study with the algorithm of discontinuation of therapy, based on biomarker evidence of clearance of the target engagement, very innovative. From the efficacy readout, it did not compromise the efficacy readout for the study, so all of these are positives and support that approach.

Now, transitioning into the clinical care, there are, at least from my standpoint, two issues that need to be addressed. The duration of follow-up in the study with persistence of biomarker evidence of clearance and the clinical efficacy was relatively short in the time span of that neurodegenerative disease. So we definitely need longer duration of follow-up with defining the algorithm of reinitiation, intermittent, again, whatever the data supports.

The next operational question is, in order to make the decision to discontinue therapy, based

on my understanding -- I'm not an Alzheimer's expert, but based on everything that was discussed today -- it will require the biomarker -- specific, not categorical biomarker, but a specific biomarker -- of quantitative tau PET imaging, tau amyloid imaging. So again, they approved it is available in the community, but will it impede the decision process between the physician in the clinical practice?

So from my standpoint, I would leave it to the discussion between the particular provider -- to educate, and would leave it to the decision of the particular provider and definitely collect more information, provider, and the patient, obviously.

DR. MONTINE: Thank you.

Merit?

DR. CUDKOWICZ: It's not good to go after Tanya; we think alike. I also thought it was very innovative, and it's good for patients to not have to take medications more than they need to. I do think clinically, though, it could be challenging

for clinicians to decide when to redo the PET scan, and also it might not be available everywhere and there aren't any other other tools; so having some long-term follow-up, whether that's in the current open-label extension or in some postmarketing approach, to really get at some advice for the physicians about when to do this test and how to make those decisions. Then also in the end, at some point, do people have to restart? Those kinds of things still are lacking some information.

DR. MONTINE: Thank you.

Kathleen was next.

DR. POSTON: Kathleen Poston. When I think about the burden of a treatment for my patients, there is the side effects, and then there's the practical part of having to take the intervention, whether that is taking an oral medication once a day or multiple times a day, or having to come in for an infusion once a month. That also adds to the caregiver burden, which is part of the overall burden of disease, which we heard during the public comments.

For those reasons, both the physical challenge of taking the therapy of an infusion plus the actual risk of side effects, which we'll be discussing at a further question, I am very encouraged by the model here of looking at a biomarker for evidence of target engagement and target clearance, which was the goal of the therapy, and being able to come up with a conceptual time when that therapy does not need to be continued. So I think that is a very positive thing to have on this.

I echo my colleagues in that the two unknown questions, let's say that the amyloid test is done at a year and it's still positive, when do you test it again -- to ask that question -- and how many times do you have to keep retesting it in the future if it is not clear at the timepoint decided? Then if it is stopped, when would someone consider restarting the therapy? Neither of those questions were answered by the data presented to us today, and I think, as a provider, those are questions I would eventually want to have an answer to, to

practically implement this in clinic.

DR. MONTINE: Thank you.

Sarah, you're next.

MS. DOLAN: I am looking at this from the consumer perspective, and the outlook here is really great. I think the fact that we can discontinue, potentially, this medicine at some point when amyloid's been cleared could actually be a motivational factor for patients to stay compliant with testing, with their infusions. So I do think that it could be a compliance enhancement.

I also think patients that have been discontinued because they've cleared amyloid can celebrate that, but there always is going to be that concern in the back of their heads of, "Is it coming back? Am I getting worse?" So I do think it would be beneficial for the applicant to consider tools to give to patients that are no longer being treated but are being monitored and their care partners to watch them at home because, potentially, you could have symptoms come back before your next PET scan.

DR. MONTINE: Thank you very much.

Nilufer?

DR. ERTEKIN-TANER: Nilufer Ertekin-Taner. I agree with the need to monitor the patients for their clinical status, functional status, easily accessible biomarker status after the cessation of the treatment. By the same token, they also need to be monitored for side effects, if you will, even after discontinuation of the treatment.

We don't have information on, for example, longer term risk for ARIA or intracranial hemorrhage. We don't have information, from a long-term standpoint, on risk of, say, thrombolytics because that data and that database does not exist. And as we're collecting information on ongoing efficacy, we need to also collect information on adverse outcomes after cessation of the treatment.

DR. MONTINE: Thank you.

Colette, please.

MS. JOHNSTON: Well, a couple minutes ago, what I was going to say was new, but it's not now.

So I just want to stand by what you guys have said and back that up from a patient's perspective, especially from a rural community perspective. It is very difficult. The more tests you add and the more that we have to do, especially in a rural setting and in some very difficult ethnic settings, that adds to it. However, that said, when the caregiver is responsible for watching the patient because they've stopped the treatment, you're not always going to get all the information that you need. So I would encourage implementing some form of continuing to monitor in some way, and maybe that's simply phone calls to the caregiver and to the patients themselves.

I love the idea of being able to stop a treatment, and keeping track of it, and not overdosing our patients. All of that is, I think, innovative and new, and I love seeing that perspective from the clinicians. From the patient's point of view, that is something we don't hear a lot of, and that gives them something to strive for. It also gives caregivers a platform to

work from. But I am concerned about what happens if we're not following up and we're not getting that information once we discontinue the dosing.

DR. MONTINE: Daniel?

DR. PRESS: Dan Press. Just a quick point, it will also help access from the point of infusion capacity. It turns out infusion capacity at many hospitals is a rate limiting step for administering these therapies, and the fact that this is once a month; the fact that it can be administered over half an hour; the fact that the watch time afterwards is only half an hour instead of 4 hours; and the fact that we could potentially stop it when someone is amyloid negative will allow more patients to get treated.

DR. SIMUNI: Tanya Simuni. I just wanted to build on what Dr. Press has said. I think that implicit in all this discussion, if truly the data demonstrates that elimination of the target protein accumulation translates into persistent clinical benefit, it's a huge cost savings for the society. We're talking about expensive treatment, expensive

surveillance, so again, that is hugely important building on the access, but the cost to be provided, that it is supported by long-term postmarketing data.

DR. MONTINE: Costantino?

DR. IADECOLA: Costantino Iadecola. I think the advantage of using the lack of amyloid to stop the drug is a great thing because we don't need treatment, but that raises the question of if the disease starts again, when are you going to have to intervene? The post-treatment trajectory is unknown. It may vary from patient to patient. For example, what happens to the APOE ε4 ones? We'll have a faster accumulation. What about co-existing vascular morbidity that may also accelerate the deposition and so on? So monitoring is going to be necessary; now, at what level? Leave it to you guys to decide, but it obviously needs to be. Then considering that amyloid accumulates 20 years before you start to have committed impairment, that's also another question. How quickly, how soon, are you going to have to intervene if you

have a signal of amyloid going up?

DR. MONTINE: Dean?

DR. FOLLMANN: Not much to add. It's been a really good discussion I think. One thing I was interested in was the people who don't achieve clearance, they're kind of interesting, and it'd be, I think, worthwhile to do analyses to try and find factors why they don't clear the amyloid plaques. Also thinking in the future, though, there's probably an opportunity to do repeated cycling of this after the initial infusions, or initial cycles of infusions, tested again later, and I'm sure Lilly is planning to look at that, and it'll be interesting to see the studies that come out.

DR. MONTINE: Thank you.

Cindy?

DR. CARLSSON: I think related to that, I know I brought this up before -- this is Cindy Carlsson -- if there's some way that we can continue -- and I know maybe this is outside of this discussion, but trying to use CSF for blood or

other measures that move us away from the PET scans because, really, starting the therapies and ending the therapies is going to really depend on if people have access to amyloid PET scanners, which not all communities do. So that access issue is still kind of lingering.

DR. MONTINE: Thank you.

Well, if I may then, the committee felt this was an innovative component of the trial. It provides a lot of useful information, hope even, useful for patient management, for patient compliance, patient motivation, and even societal benefits, so a very useful component of this study.

Because it's innovative, it raises a lot of questions, questions around the duration of the benefit; how do you monitor the patients during this interval between drug stopping and potentially restarting; how do you make the decision to restart; what tests or tests do you use; and what will it mean for potential side effects by starting, stopping, and restarting again?

We just don't know the answer to any of

these things, so work to be done, obviously. But again, my feeling from listening to the comments, the committee feels this is an innovative and very positive outcome of the way the trial was designed.

Any further comments on this discussion point?

(No response.)

DR. MONTINE: Okay.

So we're going to move on then to question 4. Number 4 is, again, a discussion point. Discuss the overall benefit-risk assessment of donanemab for the treatment of Alzheimer's disease. If the available evidence supports a benefit, discuss if the risks appear to be acceptable given the observed treatment benefit and if there are subgroups of patients for whom the benefit-risk would be more or less favorable.

Any questions around the wording of this discussion point?

(No response.)

DR. MONTINE: Hearing none, then we'll start the discussion.

DR. ERTEKIN-TANER: Nilufer Ertekin-Taner. Based on the data presented, there was acceptable risk-benefit for APOE epsilon 4 lacking individuals and APOE epsilon 4 heterozygote individuals. There wasn't a statistically significant clinical benefit for the APOE ε4 homozygote individuals who also appear to be at the highest risk for the side effects. So for this subset, the risk-benefit ratio is less favorable. It would be very important for the patients and the caregivers to have a very clear understanding of this and to have wording information to reflect this.

The other thing to re-emphasize is the need to have patient-specific and subtype-specific risk categorization in very clear terms. This is essential for care providers, in general, to be able to make informed decisions and for patients and their caregivers to make informed decisions. So I'll stop there.

MS. DOLAN: I'm going to follow up quick on this because I just want to say, "Ditto. Thank you." And I can't say everything that she said, so

we're just going to leave it with her. But my job here is as the patient advocate, and I am not, gratefully, a patient of Alzheimer's, but I have been a caregiver for multiple family members for over 15 years. We didn't have this option. We didn't have anything even close to this.

So when you talk about risk and benefit, there are two words there; and yes, there is risk. But when you get a diagnosis of Alzheimer's, you don't have anything but risk. But for those that are suffering now and those caregivers -- who you can't imagine until you walk in their shoes what they do -- there is a benefit. And the biggest benefit you can give anybody as an Alzheimer's patient or a caregiver is time, time to be with their loved ones; time to make decisions; time to bring their family in; time to get organized.

What I see here, it's a drug. Every drug has a risk. You can take an aspirin and it can have a risk. But we live in a society now where we get to have clinicians, and caregivers, and family members help us make choices, and it's up to the

patient to be their own advocate and have their own advocates there to really research those risk-benefit ratios. And in this case, if I would have been given this option with my father, I absolutely would have prayed that he qualified because if you could have bought me the time to have in the beginning, when the onset of his disease hit, it would have been the greatest gift I could have had at the time.

So when you think of risk-benefit, we tend-- and I live in a scientific world; my day-to-day life is a scientific world -- to look at it as scientists, but my role here is to get you to look at it as patients and caregivers. So inasmuch as it is not perfect, it is acceptable as far as I'm concerned.

DR. MONTINE: Thank you.

Cindy?

DR. CARLSSON: Yes. I think we've had a lot of discussion about the benefits in different capacities here, and as far as the risks go, it seems like there have been some very clear

parameters that we could put in place regarding discussions around APOE ε4 and extra MRI scans, so the monthly MRI scans up front; looking at baseline MRI scan risks; the siderosis, superficial siderosis; and other microhemorrhages. It seems like there are some good safeguards that could be put in place.

I agree with others who have said having a personalized risk profile, but again, I know a lot of my colleagues in geriatrics are concerned because you have frail older adults, and you want to first do no harm but, again, I think there are also some very brisk older adults and younger adults -- we've heard of people in their 50s-60s developing dementia -- who deserve that chance to have a discussion with their clinician and really weigh those risks and benefits because I think we all know that our patients have different values they attach to different benefits. Some are willing to take those risks; some don't want to interrupt their fishing to come in for infusion. So again, I think those risks-benefits really

should come back to the patient and clinician.

I know another concern that a lot of my colleagues in geriatrics have is if you have a person who's elevated amyloid but maybe they have no tau. What if that cognitive change is really from something else? So their MCI is from sleep apnea or something else. That I think comes back to making sure that we have good educational procedures in place to make sure that clinicians are diagnosing a true MCI. I think it falls outside of the approval of this. It's up to the clinicians to have the right training to make sure they're diagnosing the MCI correctly so they're not treating someone who is asymptomatic elevated amyloid with this therapy until we have the prevention studies available. So I think that the overall benefit-risk ratio is acceptable.

DR. MONTINE: Thank you.

Kathleen, you're next.

DR. POSTON: Kathleen Poston. When I think about risk to benefit, one of the things I keep in mind is the heterogeneity of the patient

experience, and the experience of many ε4 homozygotes is a younger age of onset and is a bit of a more ominous progression of their dementia. I agree that the risk in the ε4 homozygotes, in the small group that were included in the study, was higher, particularly of both ARIA-E and ARIA-H.

This is also a group who are experiencing the disease, for many of them, at a different stage in their life. They are looking at, again, a faster progression. So I think that this idea of the individualized weighing of risk and benefit within the context of the physician being educated as to knowing this balance is going to potentially be different for an ε4 homozygote versus a non-carrier.

There's a lot of education that needs to go on around that so that the patient, their family, and the physician can do that shared decision making together and have one person decide. Maybe they're younger and they don't want to take the increased risk of ARIA-H because of that. Someone else might be younger and say that's why I want to

take that risk, and it depends on their personal situation.

So I do think there's going to have to be a lot of education around this because that risk to benefit, the risk is greater, but then also the personal situation of the patients is going to be different.

DR. MONTINE: Just one second, Daniel.

Sarah's next, and then Daniel.

MS. DOLAN: I think that another word we need to add, another R word, is "responsibility." If we're going to take risks, if we're going to allow a medicine to have risks associated, then we need to be responsible. And one of the ways we can be responsible is to arm and educate these folks -- the patients, and the caregivers, and the physicians -- with materials that they can take with them should there be an emergency. What if someone does think they're having symptoms of stroke? They can take an information card, not just I'm on this drug, but have an information card about the risks associated with getting a certain

treatment at the ER because I'm on this drug.

I do believe that we need to think responsibly if this medicine is going to come to market because there are the risks associated. The caregivers need to understand what to look for at home if there is something happening, if there is an AE that's taking place, and who to call, and what to do. So those are my two cents about risks.

DR. MONTINE: Thank you.

Daniel?

DR. PRESS: I largely agree with everyone on safety issues, but I would also point out that I'm concerned about the efficacy in ε4 homozygote people. This is the second medicine in the class now, neither of which have been able to show efficacy in ε4 homozygotes, and in fact, it's really been right around the line of no effect at all.

So I hear others that patients should have the right to take a therapy that has a potential benefit even if it has risk, but if there isn't any benefit, then that's a real concern. I'm not

saying that we shouldn't offer it to them, but I'm saying that we should perhaps even in the label emphasize both the point that there's a significantly higher safety concern and there's less evidence for efficacy.

DR. IADECOLA: Yes, and the other thing is the ethnicity, race. We need to know more, whether it's worth treating the Hispanic and the benefit ratios there.

DR. MONTINE: Thank you.

Tanya?

DR. SIMUNI: Not to be redundant to the previous discussion or question about it, the therapeutic here has class risk, which is on-target risk. I think that all of us agree that the benefit-risk ratio is favorable.

I just wanted to comment on the second part of the question, of the individuals who have higher benefit-risk ratio versus the lower benefit-risk ratio. The data supports that individuals with low-moderate amyloid levels have better clinical endpoints, and that, to a certain degree,

corresponds to what Cindy was saying, tremendous importance -- provided the therapeutic is approved -- education of the providers and the community because the general trend is you have mild symptomatic syndrome; why do you want to take the risk? Again, I don't want to extrapolate on that, but I think that that should not be lost in that domain of education.

DR. MONTINE: Thank you.

DR. FOLLMANN: Yes. Dean Follmann, just a couple of additional comments. One is the APOE ε4 epsilon positive homozygotes. If you look at the treatment effect there, to me it looks similar, numerically less but similar, to the other groups. The studies aren't powered to look at those separately, so I would say there's not evidence that they differ a lot; and just because that confidence interval includes the null value for the small subgroups, I don't want to over-interpret that they're not getting a benefit.

The other subgroup I wanted to talk about is low or no tau, and as I mentioned earlier, the

benefit they derive might be less because it takes longer for that benefit to be realized, so less benefit if you look at it over a time scale horizon, and yet the risk would be the same. That's a point I want to make.

Also the issue of timing, it could be that it's better to wait a while to get the biggest benefit of the drug as opposed to starting it as early as you can. Early as you can maybe will prevent Alzheimer's; maybe it won't. Maybe it will induce a reaction that makes the human refractory, or develop ADA, or whatever, so you've used the drug at a time when it wasn't optimal to use. So I think further study of this to understand can we keep giving it or is there an optimal time will be important to do.

DR. MONTINE: Thank you.

Excuse me. Kathleen again.

DR. POSTON: Sorry. I forgot something. Kathleen Poston. When I think about risk, another thing that I keep in mind is the burden of monitoring that risk; and that is not insignificant

here, particularly if it is numerous MRI scans that are required in elderly dementia individuals who don't always do the best with MRI scans, and particularly in rural areas where it's harder to get MRI scans. But then also the interpretation of those MRI scans there. It's not a black and white, super easy thing to always interpret these scans. If areas don't have access to a neuroradiologist, they might have challenges knowing what's normal for age versus what's changed and could be evidence of ARIA. So again, I think education around the interpretation of monitoring risk needs to be taken into consideration because it's non-trivial.

DR. MONTINE: Thank you.

Merit, please.

DR. CUDKOWICZ: I wanted to maybe comment on what Dean just mentioned about the low or no tau, that these are still people with MCI. They just don't meet the tau PET definition of having tau, but my understanding is they still have tau, and they did have lowering of amyloid and about the same risk of ARIA. So I'm not worried about the

risk-benefit ratio in that group, and I agree with what my colleagues have said about the APOE ε4 homozygotes.

DR. MONTINE: Thank you.

So I'll try to summarize our discussion. There were two parts to this discussion. One was the overall benefit-risk and then to discuss subgroups. We didn't spend much time, overall, but I believe it's the sense of the committee that, overall, the benefit-risk ratio is positive. We spent most of our time talking about subgroups, principle one.

Principle two we discussed first was APOE ε4 homozygotes, where there may be less benefit, although I'm not sure that everyone agreed on that point. But there may be less benefit with a fixed risk, so the benefit-risk ratio may be different in that subgroup. The other group that was mentioned a few times was underrepresented individuals, historically underrepresented individuals who were also underrepresented in this study, and just really a lack of the data to know, so we need to be

cautious about that group as well.

For both of those, the apparent consensus of the committee is that provider and community education will be very important so that everyone's clear on benefit versus risk if they're in one of these subgroups and then they make their decision with their provider.

The third subgroup that was discussed was the no/low tau group, and there the question is, is this a group where the risk is fixed but the benefit is perhaps lower? And we had a discussion, so I'd say there's not a consensus from the committee around that point. We had a discussion around that point.

Any comments on my summary?

DR. PRESS: I would just say there's a lack of data on the very low and no tau, is the problem.

DR. MONTINE: Thank you, Dan.

May we please go to the next question? So this is our second vote. Do the benefits outweigh the risks of donanemab in the treatment of AD in the population enrolled in the clinical trials with

mild cognitive impairment and mild dementia?

Let me read that last point again because I stuttered. In the clinical trials with mild cognitive impairment and mild dementia, explain the rationale for your vote. If you voted no, provide recommendations for additional data or analyses that may support a conclusion that the benefits outweigh the risks.

For our voting members, it's on the panel in front of you, so please vote.

DR. SEO: Actually, I'm sorry, Dr. Montine, to interrupt. Perhaps we can first check if the panel members have any questions about the clarity or wording of the question.

DR. MONTINE: Thank you. Excuse me.

Any questions about the wording?

(No response.)

DR. MONTINE: Then we can proceed to vote.

(Voting.)

DR. MONTINE: Just a few seconds, and we'll display the vote.

DR. SEO: This is Jessica Seo, DFO. I'll

read the results into the record. There were 11 yeses, 0 noes, and 0 abstentions.

Dr. Montine?

DR. MONTINE: Now that the vote is complete, we will go around the table and have everyone who voted state their name and then their vote, and if you want, you can state the reason why you voted as you did into the record, although in the opposite order.

Cindy, is it ok we start with you?

DR. CARLSSON: Cynthia Carlsson. I voted yes. Again, we've talked about the benefits of the therapies. I think for the group that was included, the risks can be safely clarified with the proposed MRI program. The training and making sure there's enough access to MRIs falls outside of the purview of this group for training, and then the healthcare systems, make sure they have those safety measures in place. The question was in the population enrolled in the clinical trials, so again, we don't know about the risks and benefits for those who are not enrolled, as we've mentioned

before, underrepresented groups and Down syndrome patients.

DR. IADECOLA: This is Costantino Iadecola. I voted yes because I think the benefits outweigh the risks, and if there are some subgroups where further analysis is required, this should not hold up to make this drug available to the public.

DR. PRESS: This is Dan Press. I voted yes for the same reasons as stated.

DR. SIMUNI: This is Tanya Simuni. I voted yes based on the data that was provided and discussed, obviously with appropriate risk mitigation and surveillance.

DR. CUDKOWICZ: Merit Cudkowicz. I voted yes for the same reasons as my colleagues.

MS. DOLAN: Sarah Dolan. I voted yes for the reasons stated prior.

MS. JOHNSTON: Colette Johnston. I voted yes for the reasons I've already stated. I do like the innovation of this, and I would encourage them to gain more information in the areas of weakness that have been stated also.

DR. MONTINE: Thank you. Thomas Montine. I voted yes for the reasons already given by my colleagues.

DR. POSTON: Kathleen Poston. I voted yes that the benefits outweigh the risks as long as the risks are being monitored and educated upon appropriately.

DR. FOLLMANN: Dean Follmann. I voted yes for the reasons given already.

DR. ERTEKIN-TANER: Nilufer Ertekin-Taner. I voted yes for the reasons stated. We need more data and longer surveillance, especially more data in African Americans; Latino Americans; Down syndrome; autosomal dominant AD; and ε4 homozygotes.

DR. MONTINE: Thank you, everyone.

Before we adjourn, are there any last comments from the FDA?

DR. BURACCHIO: I would like to thank the committee for your wonderful input today. It has been very informative and very helpful for us. We will take your comments and suggestions to heart as

we go back to weigh on our final decision. Thank you.

Adjournment

DR. MONTINE: Thank you. Thank you for organizing the day. Thank you, Dr. Seo, so much for a perfect meeting. Thank you, all the committee members. We are adjourned.

(Whereupon, at 3:55 p.m., the meeting was adjourned.)