FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

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

Virtual Meeting

Friday, November 6, 2020
10:00 a.m. to 5:06 p.m.
Meeting Roster

ACTING DESIGNATED FEDERAL OFFICER (Non-Voting)

LaToya Bonner, PharmD
Division of Advisory Committee and Consultant Management
Office of Executive Programs, CDER, FDA

PERIPHERAL AND CENTRAL NERVOUS SYSTEM DRUGS

ADVISORY COMMITTEE MEMBERS (Voting)

G. Caleb Alexander, MD, MS
Professor of Epidemiology and Medicine
Johns Hopkins Bloomberg School of Public Health Center for Drug Safety and Effectiveness
Baltimore, Maryland

Nathan B. Fountain, MD
(Chairperson)
Professor of Neurology
Director, FE Dreifuss Comprehensive Epilepsy Program
University of Virginia
Charlottesville, Virginia
Dawndra Jones, DNP, RN, NEA-BC
(Consumer Representative)
Chief Nursing Officer, VP Patient Care Services
University of Pittsburgh Medical Center
McKeesport Hospital
McKeesport, Pennsylvania

Aaron S. Kesselheim, MD, JD, MPH
Associate Professor of Medicine
Harvard Medical School
Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine
Brigham and Women’s Hospital
Boston, Massachusetts

Richard J. Kryscio, PhD
Professor, Statistics and Biostatistics
University of Kentucky
Sanders-Brown Center on Aging
Lexington, Kentucky
Chiadi U. Onyike, MD, MHS
Associate Professor of Psychiatry and
Behavioral Sciences
Division of Geriatric Psychiatry and
Neuropsychiatry
Department of Psychiatry and Behavioral Sciences
The Johns Hopkins University School of Medicine
Baltimore, Maryland

Joel S. Perlmutter, MD
Elliot Stein Family Professor of Neurology
Professor of Radiology, Neuroscience,
Physical Therapy & Occupational Therapy
Washington University School of Medicine
St. Louis, Missouri
PERIPHERAL AND CENTRAL NERVOUS SYSTEM DRUGS

ADVISORY COMMITTEE MEMBER (Non-Voting)

Michael Gold, MS, MD

(Industry Representative)

Vice-President

Neurosciences Development

AbbVie

North Chicago, Illinois
TEMPORARY MEMBERS (Voting)

John Duda, MD
BLR&D Senior Clinical Research Scientist
National Director, Parkinson’s Disease
Research Education and Clinical Centers,
Chairperson, National VA Parkinson’s Disease
Consortium,
Director, Parkinson’s Disease Research,
Education and Clinical Center and
Co-Director, Center for Neurotrauma,
Neurodegeneration and Restoration at the
Michael J. Crescenz VA Medical Center in
Philadelphia and
Associate Professor of Neurology,
Perelman School of Medicine at the University
of Pennsylvania
Philadelphia, Pennsylvania

Scott Emerson, MD, PhD
Professor Emeritus of Biostatistics
University of Washington
Seattle, Washington
Richard P. Hoffmann, PharmD
(Patient Representative)
Retired Pharmacist/Medical Writer
Patient Advocate/Parkinson’s Foundation
Hernando, Florida

Madhav Thambisetty, MD, PhD
Senior Investigator and Chief
Clinical and Translational Neuroscience Section
Laboratory of Behavioral Neuroscience
National Institute on Aging
National Institutes of Health
Adjunct Professor of Neurology
Johns Hopkins University School of Medicine
Baltimore, Maryland
FDA PARTICIPANTS (Non-Voting)

Eric Bastings, MD
Acting Director, Division of Neurology I
Deputy Director, Office of Neuroscience (ON)
Office of New Drugs (OND), CDER, FDA

Teresa Buracchio, MD
Deputy Director
Division of Neurology I
ON, OND, CDER, FDA

Billy Dunn, MD
Director
Office of Neuroscience (ON)
OND, CDER, FDA

Sally Jo Yasuda, PharmD
Safety Team Leader
Division of Neurology I
ON, OND, CDER, FDA
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*A Matter of Record*

*(301) 890-4188*
PROCEEDINGS

(10:00 a.m.)

Call to Order

DR. FOUNTAIN: Good morning, and welcome. I'd first like to remind everyone to please mute your line when you're not speaking. For media and press, the FDA press contact is Lindsey O'Keefe. Her email and phone number are currently displayed. My name is Dr. Nathan Fountain, and I'll be chairing this meeting. I will now call the November 6, 2020 Peripheral and Central Nervous System Drugs Advisory Committee meeting to order. Dr. LaToya Bonner is the acting designated federal officer for this meeting and will begin with introductions.

Introduction of Committee

DR. BONNER: Good morning. My name is LaToya Bonner, and I am the designated federal officer for today's meeting. All voting members have confirmed via email that they have reviewed the prerecorded presentations for today's meeting in their entirety. When I call your name, please
introduce yourself by stating your name and affiliation, and "I confirm."

I will start with Dr. Alexander. Please state your name for the record and your affiliation.

DR. ALEXANDER: Caleb Alexander. I'm a professor of epidemiology and medicine at Johns Hopkins Bloomberg School of Public Health, and I confirm.

DR. BONNER: Next is Dr. Fountain.

DR. FOUNTAIN: Nathan Fountain. I'm a professor of neurology and chair of the Comprehensive Epilepsy Program at the University of Virginia, and I confirm.

DR. BONNER: Next is Dr. Jones.

DR. JONES: Good morning. Dawndra Jones, chief nursing officer, vice president of patient care services at UPMC McKeesport hospital, and I confirm.

DR. BONNER: Thank you.

For the record, Dr. Gold, please introduce yourself and your affiliation.
DR. GOLD: Hi. This is Dr. Michael Gold. I am vice president and head of neurosciences development at AbbVie. I'm a neurologist, and I'm the nonvoting industry representative, and I confirm.

DR. BONNER: Thank you, sir.

Dr. Kesselheim?

DR. KESSELHEIM: Hi. My name is Aaron Kesselheim. I'm a primary care doctor and professor of medicine at Harvard Medical School and a faculty member in the Division of Pharmacoepidemiology and Pharmacoeconomics Brigham and Women's Hospital, and I confirm.

DR. BONNER: Thank you, sir.

Dr. Kryscio?

DR. KRYSCIO: Yes. Good morning. I'm Richard Kryscio, professor of statistics and biostatistics at the University of Kentucky, and I confirm.

DR. BONNER: Next is Dr. Onyike.

DR. ONYIKE: Good morning. I'm Chiadi Onyike. I'm a neuropsychiatrist and a psychiatric
epidemiologist, and an associate professor of psychiatry and behavioral sciences at the Johns Hopkins University. I confirm.

DR. BONNER: Thank you, sir.

DR. PERLMUTTER: I'm Joel Perlmutter. I'm at Washington University and professor of neurology, radiology neuroscience, and I confirm.

DR. BONNER: Next we have Dr. Duda. Please state your name and your affiliation for the record.

DR. DUDA: I'm Dr. John Duda. I'm a neurologist specializing in Parkinson's disease and Lewy body dementia at the Michael J. Crescenz VA Medical Center in Philadelphia and the Perelman School of Medicine at the University of Pennsylvania. I confirm.

DR. BONNER: Thank you, sir.

Dr. Emerson, please state your name for the record.

DR. EMERSON: Scott Emerson. I'm a professor emeritus of biostatistics at the University of Washington in Seattle, and I can
confirm.

DR. BONNER: Next is Dr. Hoffmann.

DR. HOFFMANN: Good morning. I'm Richard Hoffman, the patient representative for this meeting. I'm a retired pharmacist and medical writer, and also the care partner for my wife who 14 years ago was diagnosed with Parkinson's disease, which is the second most common neurodegenerative disease next to Alzheimer's.

With regards to Alzheimer's disease, I've had numerous friends and relatives die with Alzheimer's disease or other forms of dementia over the years, and I myself have two copies of the ApoE4 genotype, which is a major risk factor for developing Alzheimer's disease. Thank you, and I confirm.

DR. BONNER: Thank you, sir.

Dr. Thambisetty?

DR. THAMBISETTY: Good morning, everyone. Madhav Thambisetty. I'm a neurologist, a senior investigator, and chief of the Clinical and Translational Neuroscience Section at the National
Institute on Aging. I'm also an adjunct professor of neurology at the Johns Hopkins University School of Medicine.

DR. BONNER: Thank you, sir.

Next we will have the FDA participants. Please state your name for the record. We'll start with Dr. Dunn.

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

DR. BONNER: Dr. Bastings?

DR. BASTINGS: Good morning. This is Dr. Eric Bastings. I am deputy director of the Office of Neuroscience and acting director of the Division of Neurology I at FDA.

DR. BONNER: Thank you.

Next we have Dr. Buracchio.

DR. BURACCHIO: Hi. I'm Teresa Buracchio. I'm the deputy director for the Division of Neurology I.

DR. BONNER: And last is Dr. Yasuda. Please state your name for the record and your -- go
ahead.

DR. YASUDA: I'm Sally Jo Yasuda. I'm the safety team leader in the Division of Neurology I.

DR. BONNER: I will now turn the meeting back over to the chair. Dr. Fountain?

DR. FOUNTAIN: For topics such as those being discussed in this meeting, there are often a variety of opinions, some of which are quite strongly held. Our goal is that this meeting will be a fair and open forum for discussion of these issues and that individuals can express their views without interruption. Thus, as a gentle reminder, individuals will be allowed to speak in the record only if recognized by me, 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 form of the meeting. We are aware that members of the media are anxious
to speak with the FDA about these proceedings, however, the FDA will refrain from discussing the details of this meeting with the media until its conclusion. Also, the committee is reminded to please refrain from discussing the meeting topic during breaks or lunch. Thank you.

Dr. LaToya Bonner will read the Conflict of Interest Statement for the meeting.

Conflict of Interest Statement

DR. BONNER: Thank you.

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

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

FDA has determined that members and temporary voting members of this committee are in compliance with federal ethics and conflict of interest laws. Under 18 U.S.C. Section 208, Congress has authorized FDA to grant waivers to special government employees and regular federal employees who have potential financial conflicts when it is determined that the agency's need for a special government employee's services outweighs his or her potential financial conflict of interest or when the interest of a regular federal employee is not so substantial as to be deemed likely to affect the integrity of the services which the government may expect from the employee.

Related to 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 application 761178, for aducanumab
solution for intravenous infusion, submitted by
Biogen Incorporated, for the treatment of
Alzheimer's disease. This is a particular matters
meeting during which specific matters related to
Biogen'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, no conflict
of interest waivers have been issued in connection
with this meeting. To ensure transparency, we
encourage all standing committee members and
temporary voting members to disclose any public
statements that they have made concerning the
product at issue.

With respect to FDA's invited industry representative, we would like to disclose that Dr. Michael Gold is participating in this meeting as a nonvoting industry representative, acting on behalf of regulated industry. Dr. Gold's role at this meeting is to represent industry in general and not any particular company. Dr. Gold is employed by AbbVie Pharmaceuticals.

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

I will now turn the meeting back over to the chair.
DR. FOUNTAIN: Thank you.

We will proceed with FDA introductory remarks from Dr. Billy Dunn, the director of the Office of Neuroscience.

Dr. Dunn?

DR. DUNN: Thank you, Dr. Fountain. Could you confirm that you can hear me?

DR. FOUNTAIN: Yes, we can hear you well.

**FDA Introductory Remarks – Billy Dunn**

DR. DUNN: Thank you, Dr. Fountain, and good morning.

Welcome to our committee members and all the folks who are joining us by electronic means for this important meeting today. I want to thank the committee for your willingness to be here, your eagerness to consider the important topics we will discuss today, and your forthrightness in sharing with us your perspectives on the application under consideration.

I want to especially thank the public attendees for their commitment to developing safe and effective treatments for Alzheimer's disease.
I particularly want to note and thank those who may be affected by Alzheimer's disease who are joining us today. For those of you who have requested an opportunity to address the committee or who have provided written comments for the committee, we look forward to and are deeply appreciative of your input. Your efforts to be here are invaluable and tremendously appreciated. Thank you.

We are here to discuss, as you can imagine, the treatment of Alzheimer's disease. There is without question a profound and enormous unmet medical need for new treatments for Alzheimer's disease, the sixth leading cause of death in the United States, with recent estimates suggesting it may have moved from the fifth to the third leading cause of death in older people.

Although there are four unique drugs approved and currently marketed for the treatment of Alzheimer's disease, current treatments, valuable though they are, do not target the underlying pathology of Alzheimer's disease and have only a modest reversible symptomatic effect of
limited duration. These drugs, approved from 1996 to 2003, have been unable to alter the relentless progression of Alzheimer's disease.

Deaths from Alzheimer's disease increased dramatically, nearly 150 percent from 2000 to 2018. Even as deaths from other major diseases, including heart disease, stroke, HIV/AIDS, have decreased, we have not had a novel drug approved for Alzheimer's disease since 2003. We are highly sensitive to the urgent need for the development of new treatments for Alzheimer's disease.

Before briefly describing some of the issues we will ask you to discuss today, I want to stress that we have not made any final decisions on the approvability of this application. With that said, you have had the opportunity to review background materials, including the briefing documents and presentations from the applicant and FDA prior to today's meeting.

Today, following my remarks, you will first hear a summary presentation from the applicant reviewing important aspects of the data presented
in support of aducanumab's approval. After that, I will return to discuss the issues involved in consideration of these data. The reason we are here today is to gain your input into some of the issues we have confronted during our review process. Thank you for the substantial efforts you have made in preparing for and attending this meeting, and thank you for the important work you will do today.

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

DR. FOUNTAIN: Thank you.

Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the advisory committee meeting, FDA believes that is important to understand the context of an individual's presentation.

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

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

We will now proceed with Biogen's presentation.

DR. HAEBERLEIN: Good morning. I'm Samantha Budd Haeberlein. Can I just check that you can hear me?

DR. BONNER: Yes, we can hear you well.

Thank you.

DR. HAEBERLEIN: Thank you, Dr. Fountain. I believe I'm waiting for some slides.
Thank you.

**Applicant Presentation - Samantha Budd Haeberlein**

DR. HAEBERLEIN: Good morning. I'm Samantha Budd Haeberlein. I'm senior vice president and head of the neurodegeneration development unit at Biogen. Thank you to the committee members, the FDA, the clinical research community, and especially the patients and families who are with us today. It's my honor to provide our opening remarks regarding aducanumab for the treatment of Alzheimer's disease.

Nearly 6 million Americans are diagnosed with Alzheimer's disease, which as you just heard is the sixth leading cause of death in the United States and has devastating consequences extending beyond the patients to the families and to society. As Dr. Galasko explained in the presentation you previously received, Alzheimer's is a progressive neurological disorder characterized clinically by memory loss, behavioral symptoms, and loss of functional abilities.

Alzheimer's is a truly terrible disease.
This disease progressively robs individuals of their memories, their sense of self, and connection to family and community. In the advanced stages, patients become completely dependent. Alzheimer's is ultimately fatal in all cases. There is no available treatment that alters the course of the disease, and this is the only disease in the top 10 causes of death in the United States that cannot be prevented, slowed, or cured. There is an urgent and unmet medical need for effective treatments to change the course of disease.

We have submitted a biologics license application seeking approval of aducanumab to delay clinical decline in patients with Alzheimer's disease. The recommended dosage is 10-milligram per kilogram intravenous infusion every 4 weeks following a titration period. We are here today because aducanumab, a molecule that targets the underlying pathophysiology of Alzheimer's disease, is the first such therapeutic to show a reduction in clinical decline in patients with Alzheimer's disease. However, this important first for the
disease is set against the backdrop of some unusual circumstances.

In our prerecorded presentations and briefing book, we detailed the results of a prespecified futility analysis. We explained that the futility prediction was inaccurate and that this led to the incorrect early termination of the phase 3 studies. But when the full data was assessed based on prespecified analyses, Study 302 was robustly positive and Study 301 remained negative. We also discussed that an earlier clinical trial in a broader patient population, Study 103, had demonstrated a treatment effect on clinical and biomarker endpoints and which was supportive of Study 302.

Given these unusual circumstances, we sought the advice of the FDA. This led to four Type C meetings over 12 months. We began these discussions from the premise that Studies 301 and 302 were equally informative. Through rigorous and focused analyses, we determined that Study 302 is a robust positive study and that Study 301 is
negative but does not detract from Study 302. And on this basis the FDA advised that Biogen submit a marketing application for the approval of aducanumab.

As you know, the FDA guidance on substantial evidence of effectiveness is generally interpreted as requiring two adequate and well-controlled trials. However, the statute has more flexibility than that. The guidance includes many examples where a single adequate and well-controlled trial supported by additional evidence can meet this standard.

Study 302 fulfills these criteria. It is a multicenter trial that enrolled 1,638 patients in 13 countries. Study 302 has dose-dependent, statistically significant and clinically meaningful effects on multiple distinct endpoints of Alzheimer's disease symptomatology. It is profoundly consistent, having met the primary endpoint with a p-value close to 0.01, met all secondary endpoints, and has shown consistency across patient subgroups.
Study 302 has also demonstrated effects on multiple objective biomarkers of disease pathology. The probability of such consistency being a false positive is very small. After reviewing the data, the FDA concluded that Study 302 is robust and exceptionally persuasive. The FDA also agreed that supportive evidence comes from Study 103. It was an earlier study designed for proof of concept but was nonetheless an adequate and well-controlled study and demonstrated a positive outcome for the high dose.

Aducanumab meets a further category in the guidance, namely compelling mechanistic evidence, having demonstrated in preclinical and clinical studies dose-dependent reductions of objective biomarkers of disease pathology. The guidance points out that findings from other trials that are not consistent could weaken the overall strength of evidence. We are not ignoring Study 301. We have worked diligently with the FDA, and we sufficiently understand why Study 301 failed. With that background, I will now recap on the key information
from the prerecorded presentations.

Given the tremendous unmet medical need,
together with advances in understanding of the
disease at the molecular level, academia and
industry have been working tirelessly to bring
forward new therapies for Alzheimer's disease
patients. Designing and developing an effective
treatment requires many things to be done right.
We must target the right disease process with an
effective molecule at a dose that achieves the
right exposure, and at the right time, in the
patient's disease. We also need to find measures
of clinical outcomes appropriate to disease stage
and many more.

Many early programs in Alzheimer's disease
have failed in clinical trials. Some of these have
been anti-A beta antibodies. We have learned a lot
from these programs, both what to target, how much
to target, and which patients may best respond.
We've also benefited from advances by the research
and medical community.

New innovations, including longitudinal
cohorts rich with biomarkers such as those of ADNI and DIAN, have shaped our understanding of the disease as a continuum. They have led to the development of new tools such as amyloid and tau PET imaging, enabling us to see for the first time these pathologies in the brains of living patients, not only at autopsy.

In the discovery and development of aducanumab, these pieces were put together. Accordingly, in 2014, aducanumab was the first anti-A beta antibody to show such large and dose-dependent reduction in brain beta-amyloid pathology.

The molecular characteristics of aducanumab differ from the first generation of anti-A beta antibodies. Aducanumab, shown here as the crystal structure with the A beta peptide, has a very shallow and compact binding cleft, making only a few contacts with the A beta peptide.

This is very different from other anti-A beta antibodies such as solanezumab and bapineuzumab, and contributes to the high
selectivity of aducanumab for toxic aggregated forms of beta-amyloid, and it's low binding to non-toxic monomers. Beta-amyloid generates different forms along the aggregation pathway, from monomers into oligomers, protofibrils, and elongation of protofibrils into fibrils. Aducanumab specifically binds to the aggregated forms of beta-amyloid in this pathway.

In addition to binding and removing the aggregated forms of beta-amyloid, biophysical data have also shown that aducanumab uniquely also directly interferes with the aggregation pathway, blocking a step called secondary nucleation, and thereby also reduces the formation of oligomers, one of the highly toxic forms of beta-amyloid.

I will now review the clinical studies starting with Study 103. Study 103, although designed primarily as a safety and tolerability study, was an adequate and well-controlled study which explicitly included prespecified clinical and biomarker endpoints. Study 103 was a 12-month staggered cohort, dose-ranging study in which
aducanumab demonstrated dose and time-dependent reduction of the pharmacodynamic biomarker beta-amyloid plaque as measured by PET. On the left are selected beta-amyloid PET images from the different dosing cohorts.

In addition to removing amyloid pathology, aducanumab showed dose-dependent reduction and clinical decline by week 54, shown here on the CDR summer boxes. Although the CDR sum of boxes was an exploratory endpoint and the study was not powered on clinical outcomes, the differences from placebo were nominally significant for the 10 milligram per kilogram dose.

We also conducted sensitivity analyses on Study 103. These sensitivity analyses showed that results were very similar using the concurrently randomized placebo cohort compared with using the pooled placebo cohort. Estimates of the treatment effect also showed minimal attenuation even when using conservative approaches to handling missing data.

These results confirmed that aducanumab was
acting in patients as it had in preclinical studies by binding to and reducing the levels of brain beta-amyloid, and was the first anti-A beta antibody program to show clinical proof of concept prior to initiating phase 3. Based on these data, we conclude that Study 103 provides supportive evidence of effectiveness of aducanumab.

Study 103 applied several clinical trial innovations. Based on the success of these, many were also implemented in the phase 3 trials. The trials included patients with early symptomatic Alzheimer's disease, earlier than in previous trials of Alzheimer's disease. Testing for the presence of amyloid pathology improved the diagnostic accuracy.

We used PET in our studies, although today, CSF tests are also validated for this purpose. We learned in Study 103 that reduction in beta-amyloid pathology was detectable early and before changes in the clinical endpoints, with clinical effects being measurable at 12 months. The CDR sum of boxes were shown to be sensitive to change and
thereby validated as an appropriate endpoint in this patient population. We discussed and gained FDA support for CDR sum of boxes as a single primary endpoint through our special protocol assessment.

We learned about the profile of ARIA in Study 103, that it was dose dependent and with an incidence higher in ApoE4 carriers, and that this incidence was reduced by titration. Study 103 and the phase 3 studies included key design features to limit the potential for functional unblinding due to ARIA. In the phase 3 studies, two efficacy assessors were required for every visit and did not have access to any information about safety, including ARIA.

Ten milligram per kilogram was selected as the target dose for phase 3 based on being the most efficacious on biomarker and clinical endpoints. To mitigate ARIA, our phase 3 studies included titration to target dose, a lower dose, and doses were stratified, at least in the beginning, by ApoE4 gene carrier status.
In these next slides I will review Studies 302 and 301. In Study 302, aducanumab met its primary endpoint, demonstrating a 22 percent reduction in decline versus placebo on CDR sum of boxes at week 78 and with a p-value of 0.0120. Missing data is always a challenge, especially in long trials in Alzheimer's disease.

Our analyses had an assumption of 30 percent missing data in line with contemporary clinical trials in this population. During the conduct of the trial, we actually had only half of that degree of patient dropout. Due to the early termination, the administrative censoring takes us up to 45 percent missing data, which is 15 percent more than planned at the design stage.

We showed in the efficacy presentation that the primary results were consistent and statistical significance was retained across a variety of approaches to handling the missing data. Most notably, those 60 percent of patients who had the opportunity to complete week 78 still had a 22 percent reduction on CDR sum of boxes and with a
p-value of 0.03.

The mean change on placebo of 1.74 on CDR sum of boxes is within the range seen in contemporary Alzheimer's trials. Although this is less than the value of 2.0 that we used in study planning, this lower than anticipated placebo decline means that our results were not inflated by an unusual placebo decline. The CDR sum of boxes is an integrated scale that assesses both daily function and cognition. Each domain measures key activities of daily life and functioning that are important to patients and their families.

As you heard from Dr. Porsteinsson in the clinical perspective presentation, the magnitude of difference seen in Study 302, over the relatively short duration of the study and in an early Alzheimer's population, translates into meaningful benefits to patients and caregivers in the real-world settings of their everyday lives.

In addition to analyses to assess missing data, we assessed if baseline factors influenced the treatment effect in Study 302. In a large
global study with long enrollment, some fluctuation in baseline factors can be expected. In the analyses summarized here, we are assessing how the baseline factors such as ApoE4, baseline disease severity, and gender influence the overall treatment effect.

Specifically, we added the baseline factors if not already in the primary analysis model, along with its two-way interactions with visit and treatment and the three-way baseline factor, treatment visit interaction. These results can be compared to the primary analysis to see how the baseline factors influenced the overall treatment effect.

The results are very consistent. Baseline factors and their interactions only explained a very small amount of variability in clinical outcomes between treatment groups. Of note, in these analyses the country by treatment interaction was identified to be nominally significant, indicating there were some differences in countries. Therefore, on the next slide we
examined how the country effect influenced the overall treatment effect.

We added the country by visit, country by treatment, and country by treatment by visit interactions to the primary analysis model. Fitting these interactions resulted in a consistent treatment effect of 0.40 and with a p-value of 0.0105.

To further understand the impact of each country on the overall treatment effect, we compared the primary analysis to the otherwise identical analysis, excluding one country at a time. This had minimal impact on the treatment effect, indicating that no ex-U.S. country had a meaningful influence on the overall treatment effect.

In these analyses, the U.S. was always included. The U.S. was a prespecified region and as intended had the largest enrollment. Therefore, on the next slide we examined the treatment effect in the U.S. only.

Here are the U.S. only results for the
primary and three secondary outcomes. The
treatment effect on CDR sum of boxes is 0.55, a
32 percent reduction in decline compared to
placebo. Corresponding results on secondary
outcomes showed reductions of 28 percent and
29 percent on MMSE and ADAS-Cog13, with a
57 percent reduction in decline on activities of
daily living.

From this series of analyses assessing the
impact of various potential aspects of
heterogeneity, it is clear that baseline
demography, and illness characteristics, and other
covariates did not have a meaningful influence on
the overall treatment effect in Study 302.

Turning our attention to the overall
prespecified study results, focusing here on the
results for the prespecified secondary endpoints,
in addition to the robust significance on the
primary endpoint of CDR sum of boxes, the high-dose
arm of Study 302 met all secondary endpoints
according to our prespecified multiple comparison
approach that was included as part of the special
protocol assessment agreement with the FDA.

The reductions in decline ranged from 18 to 40 percent versus placebo, with the high dose reaching significance in every case. In each endpoint, we see a greater reduction in the high-dose group, demonstrating, as with the primary endpoint, a dose-response relationship.

As the FDA noted in the briefing book, and I quote, "The effects for the primary and secondary endpoints encompass two acceptable approaches to establish effectiveness: one, primary endpoint of CDR sum of boxes and, two, co-primary endpoint of ADAS-Cog13 and ADCS-ADL-MCI," end quote.

Principal components analyses conducted and shared with the FDA showed that these four endpoints measured different aspects of Alzheimer's disease and have minimal overlap. Hence, aducanumab reduced clinical decline across multiple assessments, which cover broad aspects of cognition and function. The internal consistency across the four prespecified clinical endpoints is exceptional. Based on the observed treatment
effect and correlations between the endpoints, the probability that these are false positive results is about 1 in 10,000.

In each study, aducanumab showed compelling reduction in brain beta-amyloid pathology, which is a pharmacodynamic marker for aducanumab and is also a characteristic pathology of Alzheimer's disease. Here in Study 302, brain beta-amyloid was measured in a large subgroup, and similar to what we saw in Study 103, there was a dose-dependent reduction in brain beta-amyloid plaque levels with a nominal p-value of 0.001.

In addition to effects on brain beta-amyloid plaques, aducanumab showed significant dose-dependent effects on biomarkers of downstream Alzheimer's pathology. Here we see phosphorylated tau, a biomarker of Alzheimer's specific pathology measured in CSF. It shows that aducanumab provides dose-dependent and nominally significant reductions. Further, total tau, a biomarker of neurodegeneration also measured in CSF, showed similar reductions.
Our analyses, based on all patients, showed significant correlations of these biomarkers with clinical changes. Taken together, the various imaging and fluid biomarker results are consistent with a direct effect of aducanumab on lowering brain beta-amyloid pathology with a subsequent effect on reducing tau pathology and neurodegeneration.

The results of Study 301 partially differ from those of Study 302. Each of the Study 301 high-dose comparisons versus placebo was not statistically significant, however, the results for the low-dose group were similar to the corresponding results in Study 302.

As in Studies 103 and 302, a time and dose-dependent reduction in beta-amyloid plaque is seen in Study 301. The mean reduction in low dose was similar to the corresponding results in Study 302, however, the mean reduction in the high-dose group was 16.5 percent less than in Study 302 and the cumulative dose in the high-dose group was approximately 10 percent lower than in
Study 302.

In addition, the effect on phosphorylated tau in the CSF was 51 percent smaller in the high-dose group in Study 301 than in Study 302 and the cumulative dose in the CSF subgroup was 20 percent smaller than in Study 302. These data provide an important insight, namely differences in actual doses received by the patients in Studies 301 and 302 contributed to the difference in results.

In summary, the results of the two phase 3 trials were partially discordant. The results were similar in the low-dose groups across clinical and biomarker measures. On initial review of the data, the FDA stated that a marketing application may be considered based primarily on the results of Study 302 as a single positive efficacy study. It was stated that resources should be brought to bear on achieving a maximum understanding of the existing data, and in particular to investigate whether the results of Study 301 may have a role in supporting Study 302 or may be understood well.
enough to not detract from Study 302; in other words, to not represent evidence that the drug is ineffective.

In collaboration with the FDA, we initiated post hoc exploratory analyses to understand the difference in results between these trials. The exploration of the data was rigorous and was based on a set of well-defined hypotheses and was to the maximum possible degree prespecified.

We looked at the potential impact of changes made during the course of the studies. We considered whether imbalances in baseline illness and demographic characteristics could have contributed to the divergence. We considered whether differences in the incidence, severity, or management of ARIA may have played a part, although the study design had included elements to limit the potential for functional unblinding, and we investigated the role of exposure to study drug.

As noted in the briefing materials, after these analyses, we and the agency concluded that the results from Study 301 do not detract from the
persuasiveness of Study 302. It's important to appreciate that "does not detract" is very different from saying "we can't ignore." Based on the totality of the evidence, demographics and baseline disease characteristics were similar between the studies and do not have a meaningful impact on the outcome of the studies.

The frequency, severity, and management of ARIA were similar between the studies. No systemic bias due to potential functional unblinding was detected. PKPD models, based on more than 3,000 patients and 50,000 PK samples, showed that the intrinsic behavior or pharmacology of aducanumab was similar in 301 and 302. The differences between the studies were largely driven by a lower exposure to 10 milligram per kilogram in Study 301 and an imbalance in a small number of highly rapidly progressing patients.

However, meaningful subgroups in Study 301 had results similar to 302, specifically in patients who were randomized to groups with the opportunity to receive 14 doses of 10 milligram per
kilogram, and there were no findings that represented evidence that aducanumab is not effective.

We now have an understanding why the high-dose arm results differed, and we can conclude that Study 301 does not detract from the persuasiveness of Study 302. This next slide shows results based on groups formed by randomization and is one of the results to better appreciate these findings.

Patients who had the opportunity to receive 14 doses of 10 milligram per kilogram had similar benefit in both studies. The three high-dose groups who were randomized to have the opportunity for the full doses of 10 milligram per kilogram were ApoE4 non-carriers before and after Protocol 4, and the ApoE4 carriers after Protocol version 4 was implemented.

When combining the data across these groups, the weighted mean in each study showed a 23 percent reduction in clinical decline relative to the corresponding placebo groups on the CDR sum of
boxes; that is the dose regimen for which we are seeking approval was efficacious to a similar extent in both studies. The discordance between the studies arose from the subset of patients who did not have access to full 10 milligram per kilogram dosing.

We conducted additional analyses based on actual doses and using different methodologies. These additional analyses were all post hoc. However, each showed a consistent result that patients in Study 301 who received sufficient doses had outcomes similar to Study 302. It's important to appreciate that we are not pushing this forward as evidence for Study 301. Study 301 is a failed study and it does not add to substantial evidence. However, we sufficiently understand why it failed such that it does not detract from the persuasiveness of Study 302.

Moving to look at a review of safety, as you have heard from Dr. Smirnakis, the safety profile of aducanumab is well characterized based on more than 5,300 person-years of follow-up for aducanumab
treated patients. This table shows the most common AEs that were also more frequent among aducanumab treated patients with a target dose of 10 milligram per kilogram. The most common AE among aducanumab treated patients was an MRI finding ARIA-E. Other common AEs were headache, brain microhemorrhage, fall, superficial siderosis, and diarrhea, two of these also being radiographically detected.

Serious hypersensitivity reactions associated with aducanumab infusion were rare with an incidence of less than 0.1 percent. There were no notable differences in the incidence of abnormal vital signs, EKGs, and clinical laboratory tests between aducanumab and placebo-treated patients.

From our studies, we have gained a deeper understanding of both the history and the clinical impact of ARIA events associated with aducanumab as well as how to manage them. As shown in this table, most patients with radiographic findings of ARIA-E were asymptomatic. When present, the most common symptoms included headache, confusion, dizziness, and nausea, and symptoms were mostly
mild or moderate in severity.

Among all aducanumab treated patients, severe symptoms were uncommon. Radiographically, ARIA-E was mainly of mild or moderate severity and transient. The majority of patients with ARIA-E remained on aducanumab or resumed treatment after temporary dose suspension.

We are committed to further characterizing the safety profile of aducanumab in the postmarketing setting. We will continue to collect safety data through routine surveillance and in the ongoing long-term clinical study called EMBARK. EMBARK is an ongoing open-label study for all eligible patients previously in aducanumab clinical trials and aims to enroll more than 2,000 patients.

In clinical practice, as in the aducanumab clinical trials, ARIA risk mitigation will be important and will include dose titration, the use of MRI monitoring, particularly during the early treatment period, and dose suspension as needed. We recognize that if aducanumab is approved, ARIA will be a novel MRI finding and clinical entity for
many clinicians and patients. Therefore, we are committed to educating prescribers, radiologists, patients, and their caregivers on the risk of ARIA and its management.

To summarize, aducanumab in Study 302 impact multiple distinct and important dimensions of Alzheimer's disease. The breadth and magnitude of effect from 18 to 87 percent is clinically meaningful. The clinical outcome measures selected for the study cover the range of symptoms experienced by patients with Alzheimer's disease and cover the symptoms that matter to patients.

In addition to reducing declines in memory and cognition, aducanumab impacts many of the items in the Activities of Daily Living scale. The 40 percent reduction in decline in the total score represents approximately 7 months more time with retained independence in the context of the 18-month trial period. Aducanumab also showed dose-dependent reduction versus placebo in the Neuropsychiatric Inventory score, which assesses behavioral symptoms such as anxiety, agitation, and
aggression, and these symptoms are very troubling for patients and their families. These benefits were observed in patients with a limited baseline severity and against a backdrop of minimal expected disease progression over this time frame.

In closing, as you've seen, after an extensive review by Biogen and the FDA, it's clear that Study 302, with support from Study 103 and compelling mechanistic evidence provided by the biomarkers, provides substantial evidence of effectiveness, and Study 301 does not detract from this understanding.

Across the three studies in patients with Alzheimer's disease who had consistent exposure to 10 milligram per kilogram, aducanumab demonstrated a reduction in clinical decline. This means that patients who responded to aducanumab were able to better function, resonate, and interact with others than the patients who received placebo.

Given the totality of the evidence, we can conclude that the benefit-risk profile for aducanumab is favorable and potentially prolongs...
patients' independence by several months, even a few years, as demonstrated in our long-term study. This matters for the patient, their loved ones, and society. Considering the tremendous unmet need and devastating nature of this disease on patients and their families, we conclude that aducanumab is an important new option for patients with Alzheimer's disease.

I have worked in industry for 20 years to bring forward a new treatment in Alzheimer's disease. I have seen the science advance, I have seen the tools and the trials evolve, and I have seen and been part of many failures. Aducanumab is different from other A-beta targeting drug candidates. It's a stepping stone for our next advances.

The tide has turned. Aducanumab is the first drug that shows efficacy in patients with Alzheimer's disease, one of the most frightening yet common diseases to afflict us. We are humbled and proud to be able to bring this therapy to this stage, and we are hopeful for an approval that will
bring this to patients and families.

Thank you again for this opportunity. The clinical experts and Biogen team members listed here are available to help address your questions, and we look forward to the discussion. Thank you.

**Clarifying Questions to Applicant**

DR. FOUNTAIN: Alright. We will now take clarifying questions for Biogen. Please use the raised-hand icon to indicate that you have a question and remember to lower your hand by clicking the raised-hand icon again after you've asked 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 for a specific slide to be displayed, please let us know the slide number if possible. Finally, it will be helpful to acknowledge the end of your question with a thank you and end of your follow-up question with, "That is all for my question," so we can move on to the next panel member.
We'll begin with a question from Dr. Hoffmann.

DR. HOFFMANN: Hello. I had a two-part question regarding patient eligibility if aducanumab is approved, and that is, would a positive amyloid PET scan be required for treatment with aducanumab? If so, would a asymptomatic, homozygous ApoE4 carrier be eligible for treatment?

Thank you.

DR. HAEBERLEIN: Thank you for your question. As I mentioned, we did test for the presence of amyloid pathology in our clinical trials, and we do believe that this assists in this early symptomatic Alzheimer's disease population to ensure an accurate diagnosis. So we will include that amyloid testing should be undertaken prior to the initiation of treatment with aducanumab.

We use PET, but there are additional modalities available today, which will make that an easier access in comparison to the use of PET previously. Technologies such as CSF are already validated, and we are excited that there is
potential for blood biomarkers to also be available in the near future.

In regards to a patient population, our studies included patients who were in the early symptomatic stages of Alzheimer's disease, so we can conclude the benefit for patients with symptoms and who were positive for the presence of amyloid pathology.

Hypothetically, given the mechanism of action of aducanumab, it's possible that a treatment effect may also be possible in earlier stages of the disease given that the disease is a continuum and given that amyloid pathology precedes symptoms by decades. However, just to restate, we do not have data in patients who are not symptomatic at this point. Thank you.

DR. HOFFMANN: Thank you. So the answer is no on the homozygous ApoE4 carrier.

DR. HAEBERLEIN: The indication that we are seeking is for the treatment of Alzheimer's disease. The clinical trial population that we had were of a disease stage of MCI due to AD or mild AD
for those patients with symptoms. Sorry. I was focusing on your question in regards to asymptomatic.

In our studies, ApoE4 carriers and non-carriers, so all genetic allelic forms of ApoE4, so including homozygotes, were in the studies, and we have concluded that we have benefit in both ApoE4 carriers and non-carriers.

DR. HOFFMANN: Okay. Thank you very much.

DR. HAEBERLEIN: Thank you.

DR. FOUNTAIN: Next we can move to Dr. Emerson.

DR. EMERSON: Thank you. This analysis seems to be subject to the Texas sharpshooter fallacy, a name for the joke of someone first firing a shotgun at a barn and then painting a target around the bullet holes. So understanding the sampling scheme for the presented results is all important.

Can you clarify the extent to which the collection of data, that is which study and what data set, was prespecified, and if they were
prespecified, if evidence of the discordant results are truly uncommon under the null hypothesis?

   DR. HAEBERLEIN: Dr. Mallinckrodt, please?

   DR. MALLINCKRODT: Craig Mallinckrodt, Biogen. We have selected the so-called final ITT data set as the primary basis. We believe this is consistent with our prespecified analyses.

   Slide up, please. In our overall investigation, you will note that we have used several data sets. We aligned early on with FDA that the intention-to-treat data set would be the primary basis for concluding efficacy of aducanumab or not. This is because we believed it most closely followed all the prespecified aspects, all the observations under double-blind conditions, and all the patients randomized, et cetera, so thereby conforming with all aspects of our prespecification.

   There are other data sets that additionally provide information such as the opportunity to complete and the uncensored analysis. So the results we are presenting today are results that
hit the bullseye after the target was painted not before the target was painted. Thank you.

DR. EMERSON: I'd like to follow up on that then. These decisions were made after you had the results that 302 and 301 were discordant, so you were selecting -- it was not prespecified at the very beginning of the trial that 302 was going to be the only study analyzed, correct? A yes or no will work there. This is a long line of questioning.

DR. HAEBERLEIN: At the beginning of the trials, statistical analysis plans, one for each of the studies, prespecified that the overall ITT population would form the primary analysis.

DR. EMERSON: In both studies.

DR. HAEBERLEIN: In both studies.

DR. EMERSON: Okay. So just doing a simple Bonferroni correction, that p-value that you're quoting at 0.012, I don't know how to correct for the idea that you are looking at something different than the futility analysis data set. I don't know how to correct for a lot of the other
decisions that you might have considered. But certainly I can correct for you looking for the minimum of two p-values in which case -- well, assuming that they're both independent, that 0.012 is not a true p-value. A true p-value would be closer to 0.0233 just adjusting for that aspect, no other multiplicity.

Have you looked at -- well, I'll go ahead and give you -- I have looked at, conditional upon deciding that we're going to go forward with this, the probability that the other study would have a one-sided -- and by the way, I gave that -- okay, I'll stick with it -- that a one-sided p-value in the other group would be 0.59 or higher, which I believe corresponds to your two-sided 0.833.

There's a 40 percent chance under the null that the other group, that the other independent study, would have a p-value that large or larger, conditional on the fact that you've gone through and selected the results after you already knew them and decided what to present.

Do you have an alternative calculation to
this idea of this 40 percent chance, this idea that it's this discordant, given the way that you sampled which results you were going to present to us, that this p-value would be wrong?

DR. HAEBERLEIN: Dr. Mallinckrodt, please?

DR. MALLINCKRODT: Craig Mallinckrodt, Biogen. First, it's important to recognize that we have only had one opportunity to declare efficacy. The futility analysis provided no opportunity to declare efficacy.

Slide up, please. When we declared futility, at that day we looked at what observations had been collected and said this is all the observations under double-blind conditions --

DR. EMERSON: Excuse me for interrupting, Dr. Mallinckrodt, but this is not the question. I'll concede that the futility --

DR. MALLINCKRODT: I'll get to the probability.

DR. EMERSON: -- yes. What I need to know is --
(Crosstalk.)

DR. MALLINCKRODT: So we don't have a multiplicity issue across data sets; that's an important aspect. When we look at the results of Studies 301 and 302, it is almost certain that the difference between the study results are not due to chance alone. We've anchored probabilities for Study 302 with its positivity across all endpoints. We understand that the differences between 301 and 302 are not due to chance alone. We have identified rapid progressors and dosing as causal reasons for the difference.

DR. EMERSON: Again, excuse me, Dr. Mallinckrodt, but p-values are meant to capture the possibility that there might be randomization imbalances. We'll come back far later to whether you can take a post-randomization variable and exclude them. I don't believe you can. You apparently believe you do with some complicity from the FDA clinical staff, though not the FDA statistician, as near as I can tell. But claiming that it's not random chance, a p-value is
calculating the random chance of randomization imbalances.

So I disagree with your statement, and my question again is, conditional upon performing two studies and coming back to the FDA when a post hoc analysis has demonstrated a nominal p-value of 0.012, which after you adjust for the multiplicity, that you didn't prespecify which of those two independent studies would do it -- would be point .0233 -- but now again, that selection pressure on only coming to us when you've got some promising results, under the null hypothesis, how often would we expect to see -- so the true null -- that the other study would have a result as discordant as we've seen here?

Again, I came up with a 40 percent chance, conditioning on what I understand to be how we came to this advisory committee meeting. Do you have an alternative calculation that is conditioning on this selection, this conditional presentation of results to this advisory committee?

DR. MALLINCKRODT: We do not have that
particular p-value. The p-values that we have are based on the prespecified analysis plan for Study 302, showing statistical significance on all the endpoints.

DR. EMERSON: Okay. But that prespecified plan was violated because you're only presenting 302, and that was not prespecified. And I will also note -- and I'll stop questioning after this. But I will come back later to this issue of your looking at these different results and what's discordant and trying to throw out post-randomization data. So I'll stop there for now. Thank you.

DR. FOUNTAIN: Okay. Thank you.

Now we'll turn to Dr. Kesselheim.

DR. KESSELHEIM: My question was about Studied 104 and 205, which appear on the FDA document or the main document at page 22, but we haven't heard much about it. And I was just wondering if those results are also part of your epi supporting evidence.

DR. HAEBERLEIN: Thank you. Study 104 was a
small study conducted in Japan, as it is important in clinical development to include Japan in late-stage clinical trials. So that was a safety and tolerability study examining a single dose and multiple dose in a very small number of individuals. You'll see that there was 21 in total. Slide up, please. So that information, which is included in our overall BNA [ph], is not part of the conversation in regards to substantial evidence of effectiveness.

Study 205 was a study we initiated to further continue to understand and work on the monitoring and mitigation of ARIA, and Study 205 had only recruited 52 patients at the time of the futility announcement and was terminated, and only a very small proportion of individuals even had more than a baseline visit at that point in time. The data from that study, the clinical study report, is part of our BNA submission, but there is no efficacy data available from that study. Thank you.

DR. FOUNTAIN: Thank you. If that answers
your question, we'll move to Dr. Onyike.

DR. ONYIKE: Thank you. Chiadi Onyike. My question I'll set aside for a moment, the idea that the post hoc analysis seeking to disqualify the observations of Study 301 are ok.

With that in mind, you've put forward certain explanations for the discordance in the results between the two studies, 301 and 302. What you haven't discussed is the possibility that the placebo groups differed. So with that in mind, I have a question for you, and maybe you could think of it probably as being in three parts.

The first is, how did the two studies compare with respect to the trajectories in the cognitive behavioral and functional measures in the placebo groups? The second thing, accepting for the moment your definition of rapid progressors, how were they distributed in these placebo groups between the two studies? Thirdly, what were the relative distributions of MCI versus AD in the placebo groups in both studies? Thank you.

DR. HAEBERLEIN: Thank you very much for
your question, for the multiple parts. First, I'll address the second two parts of your question there, so the number of individuals who were rapidly progressing in the placebo groups. If we can have the slide of numbers of rapid progressors.

You correctly point out -- slide up, please -- that the presence of rapidly progressing individuals is not only in treatment arms but are also found in the placebo arms of both studies. And here you can see that there was an equal distribution of 4 patients who had a greater than 8-point decline on CDR sum of boxes by week 78, so really a very extreme progression of those individuals. Slide down, please.

If we can take a look at the progression of the rapid progressors across each of the clinical outcome measures -- please, I'll just bring up that slide -- just to emphasize, the rapid progressors, we've used the definition on the basis of the primary outcomes since we were interested to understand what was the impact of this imbalance in rapid progressors on the outcome measures, and in
particular on the primary endpoint.

You can see here in each of the arms of both studies, the dotted line represents the placebo decline, which in both studies was within the anticipated placebo decline. I'll ask Dr. Mallinckrodt to speak a bit more about that in a second, but first just to emphasize that those individuals who were rapidly progressing, you can see their trajectories here were really quite dramatically departing from the expected or from the placebo decline. This is on a 0 to 18-point CDR sum of boxes, and 18 points on the CDR sum of boxes equates to somebody who is bed-bound, incontinent, and completely dependent. So these are really a malignant form of Alzheimer's disease. Thank you. Slide down, please.

In regards to your question on the proportion of individuals who were mild cognitive impairment due to Alzheimer's disease in each of the studies, we can bring that up here. We had a target for enrollment such that we would have approximately 80 percent individuals who were MCI
due to AD at baseline. You can see to the lower
dend of the table here, clinical stage at baseline.
In Study 301, overall there were 80.4 percent with
MCI due to AD at baseline. In Study 302, that was
81.6 percent and quite balanced across arms.

So individuals who were diagnosed at
baseline with mild Alzheimer's disease, still
having a CDR score, global score, of 0.5, they were
the minor group in the studies. The reason for
this was our belief and understanding that the
removal of pathology may have a greater benefit if
initiated earlier in treatment, but also given that
as the disease progresses, there is a greater
heterogeneity in disease progression among
individuals. So to reduce the heterogeneity in
clinical outcomes, we also were specific in the
recruitment of disease stages.

I hope that answers your question, and maybe
if Dr. Mallinckrodt could to how --

DR. ONYIKE: Before you invite him, may I
ask how these distributions in the placebo group,
MCI versus AD, look at study end?
DR. HAEBERLEIN: At the conclusion of the study, I'm not sure that I have that figure available for you. If that's important, maybe that's something I can ask my team to find and bring up at a later point, if that would be important for you.

DR. ONYIKE: Well, what it speaks to is differences in the rate of progression in the placebo group between the two studies. That's fundamentally what I'm asking about.

DR. HAEBERLEIN: Yes, I understand, but perhaps Dr. Mallinckrodt might encompass the response to that in his response on placebo decline.

DR. ONYIKE: Yes. Thank you.

DR. HAEBERLEIN: Thank you.

DR. MALLINCKRODT: Craig Mallinckrodt, Biogen. Let's bring up slides that show trends in placebo response over time and between studies. OT-17 and 18, please. Slide up.

The slide we're showing now depicts how placebo response or placebo decline changed during
the course of this study, and this is done by
cohorts of every 200 patients, approximately
one-third of which were on placebo. In both
Studies 301 and 302, we see fluctuations over time.
The line in the center of the box represents the
median, the diamond represents the mean. And you
can see in the numbers at the bottom of the slide
how these placebo means fluctuated across the
various cohorts over time, but no systematic trend
in either study.

Slide up, please. In the next slide, we'll
look at several aspects of the difference in
placebo response across the studies, starting out
by noting that baseline demographic and disease
characteristics were consistent across studies.
Placebo decline was within the range of recent
trials but slightly less than what we specifically
assumed.

Placebo decline at week 78 varied by
endpoint. We had greater decline in Study 302 on
the CDR and the ADL, but less decline in 302 on the
MMSE and similar decline on ADAS-Cog13. Perhaps
most importantly, the treatment effect for the low dose was consistent between Studies 301 and 302, suggesting differences between studies and placebo decline was unlikely to have had a major influence on the high-dose group.

So we learned two things from this. First of all, placebo decline and the differences between studies at most played a minor role in explaining the differences between studies. Secondly, the placebo decline in Study 302 was within expectation, and the positivity in 302 is not due to any aberrance in placebo decline. Thank you.

DR. ONYIKE: Thank you.

DR. FOUNTAIN: Thank you.

Next, we'll move to Dr. Thambisetty.

DR. THAMBISETTY: Thank you, Dr. Fountain. Madhav Thambisetty. I have a two-part question. The first pertains to Study 103. Unlike Studies 301 and 302, the data and results from Study 103 have been subjected to independent peer review and were actually published in 2016 in the Nature paper by Jack Sevigny and colleagues.
In Study 103, in addition to the CDR sum of box scores and MMSE, there were three other co-equal exploratory endpoints, so all of these endpoints were stated to be exploratory. In addition to the CDR sum of boxes and MMSE, there were also assessments made on the NTB, which has 9 validated components; the Free and Cued Selective Reminding Test; as well as the Cognitive Drug Research computerized test battery.

In the back-of-the-envelope calculation, this amounts to 13 tests and 4 comparisons with placebo. These analyses were done at two time points using two statistical models, an ANCOVA model and an MMRM model, and in the Sevigny et al. paper, two sets of p-values are presented, one for drug versus placebo comparisons and the other for a dose-response comparison.

The chances of type 1 error in these unadjusted comparisons are extremely high to say the least. Do you have a sense for what the risk of type 1 error would be in these exploratory analyses that were previously reported? That's my
first question, and if Dr. Fountain permits me to come back, I'll wait for the answer and then ask another question. Thank you.

DR. HAEBERLEIN: Dr. Mallinckrodt, please.

DR. MALLINCKRODT: Craig Mallinckrodt, Biogen. We do not have the specific p-values encompassing a global family of tests across the Study 103 endpoints. However, we do note, as you've seen in the sensitivity analyses, the treatment effect estimates for the CDR and MMSE, along with the A-beta results, the biomarker results, are consistent between Studies 103 and 302, and it is that consistency that forms the primary basis for our utilization of Study 103 in support of the positivity of Study 302. Thank you.

DR. FOUNTAIN: Is the follow-up question brief or related?

DR. ONYIKE: It's not related to this topic, but if you would permit me, I can go ahead and ask it.

DR. FOUNTAIN: Okay.

DR. ONYIKE: The instance of ARIA-E is
35 percent in the treatment group compared to 2.7 percent in the placebo group. I'd like to know how the diagnosis of ARIA is communicated to the patient and their caregivers. Are they told that they have brain swelling or microbleeds in the brain that require them to come in for a previously unscheduled MRI scan? And if that is the case, are they also told that they would have to keep coming back for an MRI scan until these abnormalities improve, and until such abnormalities improve, that their dose of medication or placebo would have to be held?

How is this information communicated to patients and caregivers, and do you have a sense for what their understanding is about the nature of ARIA and how it affects them scheduling previously unscheduled MRI visits? Thank you.

DR. HAEBERLEIN: Thank you.

Dr. Chalkias, please.

DR. CHALKIAS: Spyros Chalkias, Biogen.

Thank you for the question. The patients are aware of the MRI results, and then they're asked to come
back for a follow-up MRI that's done every 4 weeks to document resolution of ARIA. Thank you.

DR. FOUNTAIN: Thank you.

Dr. Hoffmann, I notice your hand is still raised. If you have another question, you can leave it up; otherwise, you could put your hand down.

Next, we'll turn to Dr. Alexander.

DR. ALEXANDER: Hi. Caleb Alexander. Thank you both to the sponsor and to the FDA for this extraordinary amount of work that went into what we're reviewing. I do want to say that it seems to me that there is an extraordinary amount of explaining around the contrary findings.

I think, Dr. Mallinckrodt, you recently said -- you used the word "causal" in referring to rapid progressors and dosing differences as explaining the failure of 301, and I don't see it. With rapid progressors, we're talking about a difference of 4 or 5 people in a group containing 500 or more, and this theory of rapid progressors was introduced I believe only post hoc. And other
methods of examining outliers, other outlier analyses, that may be more suitable, such as robust regression or trimmed means, also failed to replicate the findings of 302 in looking at 301. It reminds me a little bit of a separate committee, where there was a subset of individuals that appeared to be responding particularly well, and I think a member of the committee used the term "super responders." So I understand the appeal of trying to identify and explain away the null findings, but I don't think that the evidence is there. I'd say the same for dosing differences, and I think we'll have a chance to get into that further later today.

I want to turn then to placebo response, and while you provided some helpful information, you didn't include, I think, the graphical illustration that I think is most troublesome to me, which I'm sure you're familiar with, which was included in the biostatistical review by the FDA. I don't know if that can be presented or if you have an identical depiction of the data, but essentially
that stratifies and looks at ApoE4 positive
pre-Protocol Amendment 4 versus post-Protocol
Amendment 4.

So it's essentially limited to the PV4
carrier stratum and looks only at the stratum
effect, which was the only stratum that was
affected by the high-dose increase, keeping in mind
that this is where the biostatistical review
indicates that there's dramatic worsening in the
placebo group after this protocol amendment but no
improvement among the low-dose or high-dose groups.

So I just am wondering then, I guess the
more pointed question here is can you speak
specifically to the separation of the placebo
groups as a function of ApoE carrier status and the
Protocol 4 amendment, keeping in mind that this is
where the efficacy is purported to be demonstrable?

DR. HAEBERLEIN: Thank you for that
question, and Dr. Mallinckrodt will comment on that
particular analysis, the specific question you had
there. I just want to appreciate
your thoughts on why so much work was brought to
bear on trying to understand the partially
discordant results of Study 301.

Really, given that across the body of work
it's only the high dose in Study 301 that is
discordant, whereas we have a really quite
considerable consistency across and within
Study 302 but also across the low dose of
Study 301 -- and it was the recognition of both
what potentially Study 302 could represent in our
initial conversations with the FDA should that be
shown to be a robust study, and what that
represents is a consistent effect on multiple
clinical endpoints and multiple objective
biomarkers in different compartments measured in
both CSF and in imaging.

So it's difficult to therefore --

DR. ALEXANDER: If I could interrupt one
minute. My question was about the placebo, the
separation of the placebo curves. But I think if
you're bringing up the consistency across multiple
endpoints, it's also worth calling out another
point raised by the FDA biostatistical review, and
correct me if I'm wrong here. But I believe that
they indicated that because the low-dose primary
endpoint was not met, technically the secondary
high-dose endpoints can't be formally evaluated.
And in fact the correlation between the primary and
secondary endpoints was moderate with correlation
coefficients of 0.4 to 0.64, regardless of what
principal components analysis may have suggested.

DR. HAEBERLEIN: The correlation conducted
by the statistical reviewer was on the overall
scales of cognition and function, and given that in
Alzheimer's disease each of these domains -- so
cognition, function, behavior -- all progressed,
therefore a correlation analysis on an overall
scale level will show a correlation due to the
progression of disease.

Principal components analysis is helpful to
understand what each scale measures, and when we do
look at the individual item levels -- slide up,
please -- there are 48 individual components across
the four prespecified primary and secondary --

DR. ALEXANDER: Okay. I'm sorry to
interrupt, but I know that I --

DR. FOUNTAIN: Maybe I can interrupt you both a little bit because I think under the time available, we're probably not going to have a chance to address all these different issues. It's sort of a multiple-part question. So maybe what we could do is pick one component and ask you to reply to that one, and then maybe you could discuss the rest if we have time.

DR. ALEXANDER: Okay. Fair enough. Fair enough. Thank you. So I guess the question then still remains the separation of the placebo curves as demonstrated by the FDA biostatistical review, and the impact of that on discerning treatment efficacy post-Protocol 4.

DR. HAEBERLEIN: Thank you.

DR. FOUNTAIN: If there's a single slide that explains that, we could maybe ask you to provide a brief explanation, if you would.

DR. HAEBERLEIN: Yes. Thank you. Slide up.

Dr. Mallinckrodt, please.

DR. MALLINCKRODT: Craig Mallinckrodt,
Biogen. We're going to be looking at results by ApoE carrier status pre- and post-PV4. Let's first focus on the placebo decline column. Pre-PV4, the carriers were 1.65, and post-PV4, carriers were 1.92, both well within the anticipated placebo response for the entire study cohort.

Now, moving down to the bottom two rows to the non-carriers, the placebo decline in non-carriers was 1.47 pre-PV4, 1.11 post-PV4. Now, let's look at the differences from placebo, 0.4 in the pre-PV4 carriers, 0.48 in the non-carriers -- excuse me, in the post-PV4 group. In the non-carriers, we see that when placebo decline went down post-PV4, actually the treatment effect went up.

If we could also bring up, please, slide OT-29 to look more comprehensively at changes pre- and post-PV4. Slide up, please. This is a unity line plot, where if there was absolutely no change between a pre-PV4 outcome and a post-PV4 outcome, the points would fall exactly on the line. These are four different outcomes so they add a
slightly difference in the scale.

You see some clustering. Just about above the 1.5 mark, those are the four outcomes associated with the CDR, and you can compare the similar shape to see how that outcome varied from pre-PV4 to post-PV4. This includes looking at all of our different endpoints. We're looking at placebo and low dose because there's no anticipated reason for why low dose should change pre- and post-PV4.

Now, the points don't exactly fall on the line, but if there was some sort of systematic bias, then the data points would all be clustered on one side of the line or the other. So we've seen earlier that there were no systematic trends in placebo response. We see there's no systematic cohort effect due to PV4, and the information in the biostatistics review was based on the means for the aducanumab group. It didn't look at separation from the placebo and that's an important aspect of that analysis.

When we look more broadly across all the
data, we see no systematic trends, but that doesn't mean there isn't some cohort --

DR. FOUNTAIN: Dr. Mallinckrodt, I'm afraid --

DR. MALLINCKRODT: -- along the way --

DR. FOUNTAIN: I'd like to ask you to wrap up here.

DR. MALLINCKRODT: Thank you.

DR. FOUNTAIN: That's great. Thank you very much.

I'm sorry to cut you off and to not give the other panelists an opportunity to ask a question about this, but hopefully we can come back to it or possibly incorporate it into the clarifying questions for the FDA.

We will now proceed with FDA summary presentation from Dr. Dunn.

**FDA Presentation - Billy Dunn**

DR. DUNN: Thank you, Dr. Fountain.

I'm going to spend the next few minutes discussing some of the issues involved in the consideration of the aducanumab marketing
application and why the evidence supporting its approval appear strong.

The purpose of today's proceedings is to discuss the data submitted by the applicant with endorsement by the FDA of such submission intended to establish the effectiveness of aducanumab. Despite intense basic and clinical research and the existence of several approved therapies, there is an enormous unmet medical need for effective treatments for Alzheimer's disease, especially treatment intended to address the biological basis of the disease with a goal of favorably altering its long-term course.

Currently, approved treatments do not target the underlying pathology of Alzheimer's disease and their beneficial effects are modest and transitory. Furthermore, there are no treatments explicitly approved for the relatively earlier stage of Alzheimer's disease included in the aducanumab clinical development program.

There has not been an approval of a novel medication for the treatment of Alzheimer's disease
since 2003. Aducanumab targets amyloid-beta, the fundamental pathological hallmark of the disease. Although there have been previous failures of other drugs that have been intended to target amyloid-beta in some fashion, there are features of aducanumab's pharmacologic profile and of the design of its clinical development program that are novel and distinguish it from prior efforts with these other agents.

After promising early clinical and biomarker data emerged from the early phase Study 103, the applicant embarked upon two trials of essentially identical design, Studies 301 and Study 302. They're intended to establish the effectiveness of aducanumab. These studies were initiated in 2015. After conducting a prespecified interim analysis for futility in early 2019, the applicant terminated Studies 301 and 302 and made a public announcement to this effect on March 21, 2019.

Subsequent examination of individual study results, that included additional data that had accrued during the time that the futility analysis
was being conducted, revealed findings differed
from the results of the prespecified futility
analysis, most notably including apparently
positive results in Study 302.

The applicant promptly brought these results
to the FDA for discussion and advice on their
appropriate interpretation. After an initial
consideration of these findings, the FDA recognized
that additional work was necessary to achieve a
maximum understanding of the results and
established a collaborative plan for further
rigorous analyses of the data. These analyses
ultimately led to the FDA advising the applicant
that submission of a marketing application seeking
approval of aducanumab was reasonable.

In addition to the efficacy information that
I will focus the remainder of my comments on, an
overview of the safety profile of aducanumab was
provided in your background materials and
presentations. The safety profile of aducanumab is
acceptable for approval.

The notably long duration and thorough
nature of presubmission review affords a particularly complete consideration by the FDA of the evidence of effectiveness to be discussed at this meeting. The evidence presented by the applicant in the application in support of aducanumab's effectiveness is essentially unchanged from that which has been considered throughout the presubmission phase.

At least on my screen the slides aren't working, so I'm just going to barrel ahead here. I provided a high-level overview of the evolution of the work of aducanumab above, but I'd like to talk a little more specifically about the interactions that began in May of last year, after the applicant's March 2019 futility declaration.

As you've heard from the applicant and seen in the background materials, after declaring futility, according to the sponsors prespecified utility analysis, the sponsor moved to explore the individual study results, which included additional data that had accrued while the futility analysis was being conducted and recognized that the results
were surprising and inconsistent with what was expected from the futility analysis.

Upon conducting that exploration, it was apparent that Study 302 now appeared strikingly positive in the high-dose group on face, and Study 301, though negative, no longer demonstrated the marked worsening in the high-dose group that was seen previously. Recognizing that this was a complicated situation, the applicant promptly requested a meeting with the agency to discuss the results they were seeing. The agency granted this meeting in order to review the data with the applicant and advised them on appropriate next steps for the aducanumab development program.

Upon reviewing the data, it was immediately apparent that the results of the primary endpoint for the high-dose groups differed dramatically between studies. Although this finding naturally received a great deal of attention at the meeting, one of the important things that we immediately noted was a remarkable degree of concordance between results in the low-dose groups in both
studies. In addition, the positive results in the high-dose group --

MALE VOICE: Hi. I'm sorry. I stepped away. Please.
leave me a message and I'll call you back as soon as I can. Thanks. Bye.

DR. DUNN: Dr. Fountain, can you confirm if I was being heard there?

DR. FOUNTAIN: You were not heard for just a moment when we heard that message, otherwise we hear you fine, so the last 2 seconds.

DR. DUNN: Alright. I'll continue.

Although this finding naturally received a great deal of attention at the meeting, one of the important things that we immediately noted was our remarkable degree of concordance between the results in the low-dose groups in both studies.

In addition, the positive results in the high-dose group of Study 302 was strongly supported by the effects on the secondary outcomes in the high-dose group of that study. Taken together, it was apparent that these results on face suggested a
robust effect in the high-dose group of Study 302
and numerically intermediate effects that were
highly aligned in both low-dose groups.

Further complicating the results in the
high-dose group in Study 301 that was discordant
from the remainder of the results was the fact that
aside from the primary outcome, the secondary
outcomes were numerically quite similar to the
low-dose group. Upon initial receipt of the data,
it seems obvious that confronted with one
successful study and one unsuccessful study without
even considering the impact of the futility
declaration, a simple response would be to advise
the conduct of an additional trial.

The pattern of results I have just
described, however, was notable and demanded
further consideration. It was apparent that if the
results presented at that meeting did in fact
represent the true effect of aducanumab, it was
imperative that all efforts would be made to
understand how reliable the results were and to
achieve a maximum understanding of the data giving
rise to these results so as to determine both the
reliability and the impact of Study 301's results
on the interpretation of Study 302.

Taken on face, even on initial viewing of
the data in May of 2019, it was apparent that the
results of Study 302 -- again, taken on face -- had
the potential to represent exceptionally persuasive
evidence of effectiveness. Therefore, the FDA
proposed a collaborative effort that would be
conducted with the applicant in order to achieve a
maximum understanding of the data to inform
appropriate advice regarding the future development
of aducanumab.

I'm going to review a few of the key
regulatory interactions to ensure that the
exchanges that we had are clear. In December 16th
of 2014, we had a Type B end of phase 2 meeting
with the applicant. The meeting included
preliminary discussion regarding study population
endpoints and dosing for the applicant's two
proposed phase 3 studies, and the division
suggested a special protocol assessment for an
in-depth review of the protocols.

On September 28th 2015, special protocol assessment agreements for both Studies 301 and 302 were reached with the division, explicitly recognizing that the design and planned analysis of each phase 3 study addressed the objective necessary to support regulatory submission. This included use of the CDR-SB as the primary efficacy endpoint. CDR-SB is a scale that adequately and meaningfully assesses both daily function and cognitive effects in an integrated manner and is consistent with FDA guidance on clinical endpoints appropriate for stage 3 patients. FDA accepts this statistically significant change on an inherently meaningful instrument such as CDR-SB as evidence of a clinically meaningful effect.

On June 14, 2019, the applicant had publicly announced futility but recognized that subsequent efficacy analyses based on data available through March 20, 2019 diverged from the earlier assessment of futility. Those additional analyses led the applicant to seek a discussion with the agency of
the results of those analyses and the next steps to be taken so that they would be taken with appropriate regulatory considerations in mind.

A Type C meeting was held to discuss the applicant's analysis of the intent-to-treat, ITT, populations of Studies 301 and Study 302, including all data prior to the March 21, 2019 announcement of the termination of the studies. The FDA advised the applicant that the development of aducanumab should not be abandoned, as the available clinical data suggest the drug may be clinically active and the data do not provide convincing evidence that the drug is ineffective.

The FDA recommended further analyses of the available data should be conducted to understand the effect of early termination of the studies on the interpretability of the data and to address the partially conflicting results for Study 301 as compared with those for Study 302.

Suggestions from the FDA provided in responses sent to the sponsor in advance of the meeting included suggestions to the sponsor,
including to explore whether there may be
demographic or baseline differences between studies
that contribute to the different results in the
high-dose group of each study and a request from
the FDA to provide conditional power estimates if
non-pooled futility analyses had been performed for
each study independently.

The FDA noted that the actual dose received
by subjects may have been influenced by dose
suspension, modification, or termination for ARIA
events. In addition, protocol amendments
throughout the study modified dosing rules for the
management of ARIA and increased the high dose for
ApoE4 carriers.

FDA wondered whether there may be some, open
quotes from our records, "disadvantage," closed
quotes, conferred upon patients enrolled earlier in
the study that developed ARIA. FDA therefore
suggested performing analyses to explore the
relationship between the actual dose of aducanumab
received and clinical endpoints. FDA encouraged
the applicant to explore the relationship between
exposure, amyloid PET, and clinical endpoints.

FDA noted that performing exploratory analyses in the context of a futility declaration was a unique situation, a truly unique situation, but appropriate to maximize learnings from such a rich data set. Interpretation of the available efficacy results of both Studies 301 and 302 had been complicated by the sponsor's declaration of futility for both studies and concomitant termination of the studies.

In the agency's view, given the interim efficacy analyses for the individual studies presented by the sponsor, it would have been more appropriate if futility had not been declared for those studies. The effect of early termination of the studies on the interpretability of the observed efficacy data and associated analyses would be a matter for further detailed consideration.

Further complicating the interpretation of the available data for Studies 301 and 302 were the partially conflicting results for Study 301 as compared with those for Study 302, with particular
attention to the discordant high-dose results of each study, while at the same time noting an apparent degree of consistency of the low-dose results between the studies.

A detailed understanding, informed by plans for further analysis of the overall results and especially these discordant results, was felt to be critical to any consideration of whether 302, with or without possible support from 301 as might be determined from further explorations of the data, might provide evidence adequate to establish the effectiveness of aducanumab for the treatment of Alzheimer's disease.

It was noted that if the results of Study 302, as apparently demonstrated by the final analyses, were not confounded by the elements described above, it was possible on face that the effects of aducanumab in that study might not only be interpreted as being supportive of the efficacy of aducanumab for Alzheimer's disease but might also be considered exceptionally persuasive on several of the instruments used to evaluate
efficacy.

For the reasons described above, FDA noted that the development of aducanumab for the treatment of early Alzheimer's disease should be continued and not abandoned, as the available data suggested that the drug may be clinically active and do not provide convincing evidence that the drug is ineffective for that indication. There are also data available indicating that aducanumab is a pharmacologically active molecule as demonstrated primarily by its effects on brain amyloid.

We noted that further analyses of the available data for Studies 301 and 302 must be conducted to better understand those results, as the currently available analyses were inconclusive. It would be possible that aducanumab is an effective drug for the treatment of Alzheimer's disease. If that is so, it would be imperative that extensive resources be brought to bear on achieving a maximum understanding of the existing data.

FDA noted that given the wholly unique
situation -- that is the current state of the
aducanumab development program, a large
international, apparently rigorously conducted,
logistically complex study that was near completion
but was now terminated with a public declaration of
futility and termination and with a large but
incomplete complicated and partially discordant
data set now suggestive of the possible
effectiveness of aducanumab -- further analyses
would best be conducted as part of a bilateral
effort involving the agency and the sponsor. The
agency and sponsor, the applicant, agreed to pursue
this approach.

An important initial step agreed to by both
parties was for the sponsor to arrange for the
prompt provision of the patient-level data sets to
the agency. FDA noted that depending on the
results of additional analyses of data for
Studies 301 and 302, when viewed in conjunction
with those analyses already available, the
submission of a marketing application for
aducanumab, based primarily on the results of
Study 302 as a single positive efficacy study, may be considered and that currently available data do not suggest the future use of Study 301 as an efficacy study providing independent evidence of effectiveness.

On October 21st, we had another Type C meeting with the applicant noting that on June 14th, additional jointly agreed-upon analyses of the results of Studies 301 and 302 had been conducted by the agency and sponsor since that time. Those analyses were intended to determine whether early termination of Studies 301 and 302 may have impacted the interpretation of efficacy data for those studies and to understand the consistency of and differences in the efficacy results of Studies 301 and 302. Based on these analyses, the FDA agreed that the results of Studies 301 and 302 were interpretable and suitable for additional consideration.

Accordingly, and in the context of the unique nature of the conclusion of Studies 301 and 302, the sponsor was informed that they had
presented on face the results of a trial of aducanumab in the treatment of Alzheimer's disease that met its primary endpoint. That would be Study 302. Equally it was noted the sponsor had presented on face the results of a trial of aducanumab for the treatment of Alzheimer's disease that did not meet its primary endpoint, Study 301.

The analyses conducted since the June Type C meeting had established not only the results of Studies 301 and 302 were interpretable, but on face those initial analyses suggested an understanding of the discordant results sufficient to allow for independent consideration of whether Study 302 might provide evidence adequate to establish the effectiveness of aducanumab for the treatment of Alzheimer's disease.

FDA explicitly noted that the conduct of the exploratory analyses to understand the consistency of and differences in the efficacy results of Studies 301 and 302 was not a statistical exercise that was intended to provide statistically persuasive evidence of effectiveness. It was an
exploratory exercise.

Referring to the FDA statement in the June meeting that, quote, "If the results of Study 302, as apparently demonstrated by the final analyses, are not confounded by the elements described above, it is possible that on face the effects of aducanumab might not only be interpreted as being supportive of the efficacy, but might be considered exceptionally persuasive on several of the instruments used to evaluate efficacy."

The FDA stated that it now appears that this was a reasonable characterization of the results of Study 302. FDA stated that it is critical to note they did not see the results of Study 302 as clearly unacceptable as a single trial to support drug approval. FDA further advised the planning for submission of a marketing application was a reasonable option.

On February 27th of 2020, at this meeting to discuss additional analyses and scientific questions raised at the previous meeting, the FDA noted that none of the analyses performed should be
viewed in isolation and none of the analyses were intended to provide independent substantiation of effectiveness. FDA noted that the analyses may help provide an understanding of the overall data for aducanumab and would be considered in terms of their ability to support or undermine the independent results of Study 302.

In June of 2020, on June 17th, at this meeting to discuss final presubmission activities, FDA noted that the applicant's plan to submit a marketing application that relied on the results of Study 302 to form the primary basis of a demonstration of substantial evidence of effectiveness of aducanumab appeared reasonable. It should be clear from this summary of key regulatory interactions, following the declaration of futility, that the applicant's presentation of effectiveness information is consistent with FDA guidance and advice.

Talking about Studies 301 and 302 -- so I'm going to assume that the slides are still not working and neither is my computer -- Studies 301
and 302 were multicenter, randomized, double-blind, placebo-controlled parallel group studies in patients with early symptomatic Alzheimer's disease, who are positive for brain amyloid pathology as assessed by PET. Participants had to have a baseline MMSE score of 24 to 30 and a CDR global score of 0 to 5.

The study was conducted in 181 centers globally. Randomization was stratified by site and by ApoE4 carrier status, carrier or non-carrier, and enrollment was monitored as such that 80 percent of the population included patients with a baseline clinical stage of MCI due to Alzheimer's disease. The study included an 8-week screening period, a 78-week placebo-controlled treatment period, and a safety follow-up period of 18 weeks after the final dose.

For the placebo-controlled period, patients were randomized to low-dose or high-dose aducanumab or placebo treatment in a 1 to 1 to 1 ratio. The primary endpoint was the change from baseline in CDR-SB at week 78 as discussed earlier under the
special protocol assessment.

The declaration of futility was addressed somewhat above, but when reviewing the regulatory interactions, it warrants some additional comments. An interim analysis for futility was prespecified in the study protocols and the statistical analysis plan to be performed after approximately the first 50 percent of participants in the studies had the opportunity to complete the week 78 primary efficacy assessment. The data cutoff date for the prespecified futility analysis was December 26th of 2018.

The futility analysis was based on conditional power for CDR-SB, which is the probability calculated on the data at the interim analysis that the final analysis would show statistical significance in favor of aducanumab. The studies were to be considered futile as the conditional power was less than 20 percent.

The conditional power for each study was calculated on a future estimate based on pooled data from Studies 301 and 302. The conditional power
power values were 12 percent for Study 302 and 0 percent for Study 301. As such, the probability of a statistically significant difference was below the prespecified cutoff of 20 percent. With the futility criteria met on March 21st, the applicant announced the termination of the aducanumab phase 3 program in accordance with the prespecified futility analysis.

The futility analysis was based on two key assumptions, first that the treatment effect in the two studies would be similar, and second that the treatment effect would not change substantially over time. Both of these assumptions were violated.

Because of this, after the futility announcement and in response to a subsequent FDA request, the conditional power was re-estimated for the individual studies and futility was not met using this non-pooled analysis. Therefore, although the criteria for the futility analysis were prespecified, the two key assumptions on which the futility analysis was based were invalid and
results of the futility analysis yield inaccurate predictions for the final outcomes.

Prior to the announcement of futility, the studies continued to be rigorously conducted per the clinical study protocols as planned under the assumption that the studies would continue. Therefore, at the time of futility declaration on March 21st, a larger set of protocol compliant data was available.

After the futility announcement, analysis of this larger data set using the prespecified primary analysis methods yielded results that differed from the results in the December 2018 data set. It was these results that the applicant first brought to the FDA's attention in May 2019 and what served as the basis for FDA's initial advice. In October, FDA prospectively agreed with the applicant's plan to amend the statistical analysis plan to reflect the final data set, which followed database lock in November 2019 due to ongoing scheduled protocol activities.

In May 2019, when the applicant first shared
the March 2019 ITT results with the FDA seeking the agency's counsel and expert opinion on the appropriateness and interpretation of the analyses, it was immediately apparent, given the potential import of the results, that it was critical to determine whether the data were suitable for analysis and interpretation given the premature termination of the studies.

Accordingly, virtual completion of the studies using modeling and simulation was used to explore the range of plausible outcomes if had the studies been run to completion. Two prospectively defined approaches were used to virtually complete the studies. The primary approach supplemented the existing observed data with simulated assessments for the data that were censored due to the early termination of the trials. Another approach fully simulated the studies to explore the range of plausible results if many trials like studies 301 and 302 were run from start to completion.

Overall, simulation results were highly consistent with the primary analysis of the
observed data. Similar results were obtained using all data or only data in patients who had the opportunity to complete the week 78 visit. Based on these results, the FDA and the applicant jointly concluded that the early termination of the aducanumab program did not compromise the interpretability of the efficacy results of Studies 301 and 302.

Results of the two trials were jointly concluded to be reliable and interpretable on face and reflected an accurate representation of the effects of aducanumab in those trials. As such, the data were suitable for further analysis. Thus, the final analysis results simply provide the final interpretable results of trials that were terminated early but analyzed in accordance with the prespecified analysis. The primary results of Studies 301 and 302 are the prespecified findings of the full randomized data set censored at March 20th in a conservative maneuver to avoid any possible bias from the futility announcement.

The results of Study 302 are highly
persuasive and the study appears capable of providing the primary contribution to a demonstration of substantial evidence of effectiveness of aducanumab. The primary efficacy endpoint analysis change from baseline and CDR-SB at week 78 demonstrated a statistically significant treatment effect in the aducanumab high-dose treatment arm compared to placebo, as has already been presented. The low-dose treatment arm demonstrated a numerical advantage compared to placebo but failed to reach statistical significance with a p-value of 0.09.

The results are consistent with a dose-response relationship. Statistically significant differences from placebo were observed for the high-dose treatment arm at week 78 for all secondary endpoints. The primary and secondary endpoint results were robust to departures from missing data and normality assumptions.

The treatment benefit was observed across a broad range of predefined relevant subgroups defined by demography and baseline disease-related
characteristics. Study 302 was a strongly positive study on multiple distinct and important clinical measures, robust to numerous sensitivity analyses, and supported by well-characterized biomarker data.

Beneficial effects on clinical measures are supported by evidence suggesting a dose-response relationship on clinical outcomes and by evidence of a dose- and time-dependent relationship on biomarkers of fundamental Alzheimer's disease pathophysiology, including brain amyloid burden, the primary direct marker of aducanumab's intended mechanistic effect.

Further clinical support for a benefit of aducanumab is found in the presentation of the individual domains of CDR-SB, the primary outcome, which were all consistent with the overall results, and in the significant exploratory analysis of NPI-10, which assesses clinical findings not directly evaluated by other clinical efficacy outcomes.

Study 301 failed to meet its primary and secondary objectives. Neither treatment group of
Study 301 had statistically significant differences from placebo in the primary efficacy endpoints or the secondary efficacy endpoints. Study 301 is a negative study.

Given the compelling results seen with Study 302, it is important to understand Study 301 in depth in order to decide if Study 301 detracts from the persuasiveness of that evidence given that it shares its design with Study 301. The major difference between Studies 301 and 302 was the partially divergent results, specifically the difference in the high-dose arms.

Consistencies between the trials included low-dose arms in both studies that have similar treatment effects across clinical outcomes that were intermediate in magnitude compared with the difference between Study 302 high dose and placebo. The low-dose arms in both studies had similar treatment effects on and the PK and pharmacologic properties of aducanumab did not differ between the studies.

Four areas were investigated to understand
the partially conflicting results in Studies 302
and 301: dose, baseline characteristics, ARIA, and
non-normality of the clinical data. By their
nature, these analyses were post hoc and
exploratory, and therefore carry with them the
appropriate caveats and caution in their
interpretation.

To address these concerns, any exploration
of the data was to be rigorous, limited in scope,
and based on predetermined and well-defined
hypotheses. To the maximum degree possible, the
analyses were prespecified and multiple analytic
approaches with differing strengths, limitations,
and assumptions were used. An important
distinction is that these analyses were not aimed
at obtaining independent support from Study 301.
Study 301 was a negative study.

The purpose of these analyses was to provide
maximum understanding of the partially discordant
results and to determine if this understanding
precluded independent consideration of Study 302.
The FDA agrees that any differences in demographics
and baseline disease characteristics between the studies are minor and do not appear to have a meaningful impact on the outcome of the studies.

To evaluate the potential functional and blinding due to ARIA, results based on all observations were compared with an otherwise identical analysis in which post-ARIA observations were removed. These analyses of the primary and secondary endpoints yielded outcomes similar to the primary analysis that included all data.

FDA agrees that a systematic bias due to functional unblinding caused by ARIA is not apparent. Some degree of functional unblinding was inevitable, but the applicant took steps in the protocol to minimize its impact, for instance using independent and blinded raters.

The analysis presented by the applicant must, by definition, be based on a post-randomization factor, i.e., the occurrence of ARIA, as baseline factors do not reliably predict the occurrence of ARIA. The results of this analysis do not indicate a systematic bias.
introduced by ARIA.

A small number of participants in Studies 301 and 302 had unusually rapid decline. This finding led to the investigation of the influence of rapid progressors on results. FDA agrees that the high-dose arm in Study 301 was disproportionately affected by an imbalance of rapid progressors with essentially twice the number of such patients as were present in all of the treatment groups.

The total number of rapid progressors was small such that removing them still leaves a large treatment population on which to base an exploratory analysis of treatment effect. This analysis resulted in a point estimate of the treatment effect for the high dose in Study 301 that favored aducanumab, indicating that small imbalances in the number of rapid progressors can have a relatively large impact on the magnitude of the primary and secondary endpoints using the primary analysis method.

FDA agrees with the importance of dose in
the area of investigation. The lack of adequate
dosing has been cited as a contributing factor to
the failure of previous clinical trials of
amyloid-targeting therapies, and protocols of
notable clinical trials have been amended in recent
years to significantly increase dose levels. The
importance of dose was also directly established
earlier in the aducanumab development program by
Study 103, which demonstrated a dose-dependent
reduction in brain amyloid and reduction of decline
on clinical outcome measures.

Through the implementation of protocol
amendments, exposure to aducanumab increased over
the course of Studies 301 and 302. To a lesser
extent, aducanumab exposure also differed between
the studies. It is worth noting that the FDA
division asked the applicant about the role of
dosing in preliminary comments to the June 14th
Type C meeting before any investigation of the
results of Studies 301 and 302 began.

A guiding principle of the hypothesis was
that if aducanumab is in fact effective and the
effect is dose related as in Study 302, it would follow that patients in Study 301 with adequate and consistent dosing should also demonstrate an effect on clinical endpoints. An absence of an effect in this subgroup of patients in Study 301 would diminish persuasiveness of Study 302.

Although it is impossible to fully account for all factors that may contribute to findings in subgroups formed by post-randomization factors, a variety of approaches, each with strengths and limitations, appears to show that consistent exposure to high doses of aducanumab does lead to similar treatment effects in the two studies.

Additionally, in the Study 301 high-dose group, clinical and biomarker outcomes were impacted by lower exposures to the target dose of 10 milligram per kilogram. Fewer participants in Study 301 had high exposure to 10 milligram per kilogram and more participants had no exposure to 10 milligram per kilogram than in Study 302.

Although the precise relationship between dosing and treatment effect is unknown, the
difference in various measures of aducanumab exposure between the studies is modest and dosing alone does not explain the negative finding for the high dose in Study 301. Also, there remains a subset of high dose assigned patients in Study 301 who received intermediate exposure to 10 milligram per kilogram yet failed to show a treatment effect of similar character to high dose assigned patients who received intermediate exposure to 10 milligram per kilogram in Study 302, or even as to subjects who received a low dose in either study.

FDA also acknowledges the inherent variability in clinical measures and challenges measuring clinical decline in this patient population. For these reasons, these analyses do not provide independent evidence of the effectiveness of aducanumab, but rather contribute to an overall understanding of Study 301. Taken together, multiple lines of evidence regarding both similarities and differences between Studies 301 and 302 suggest the partially discrepant results between Studies 301 and 302 are qualitatively
sufficiently well understood to allow for
independent consideration of the persuasiveness of
Study 302.

Moving to Study 103, this was a randomized, mult center study that included a 12-month
randomized, double-blind, placebo-controlled period
followed by a dose-blinded, long-term extension
period in patients with early symptomatic Alzheimer's disease who are positive for brain
amyloid pathology as assessed by PET. Participants
had to have a baseline and MMSE score of 20 to 30
and a CDR global of 0.5 or 1. The study was
conducted at 27 sites in the United States.

Doses studied in the first three cohorts, which were arms 1 to 7, were 1, 3, 6, or
10 milligram per kilogram administered every
4 weeks, specifically 14 doses over the 12-month placebo-controlled period. The randomization was
unequaled by arm and was stratified by ApoE status.
Participants in the fourth cohort, which is arms 8
and 9 comprising ApoE carriers only, were
randomized to either aducanumab or placebo during
the placebo-controlled period. Arms 8 and 9 were added to Study 103 to assess whether the incidence of ARIA can be mitigated in ApoE4 carriers by titration.

The safety and tolerability of aducanumab was the primary aim of the study. Secondary outcomes included the effect of aducanumab on brain amyloid plaque content as measured by PET, pharmacokinetics of aducanumab, and immunogenicity of aducanumab. Clinical efficacy endpoints included change from baseline in the CDR-SB and MMSE and were prespecified in the study protocol as exploratory. Rater blinding was similar to Studies 301 and 302. During the placebo-controlled period, pharmacodynamic and clinical assessments were performed at 6 months and 1 year.

Although design primarily is a safety and tolerability study, Study 103 was a rigorously designed placebo-controlled study that explicitly included assessments of prespecified clinical and biomarker endpoints and did have a prospectively identified statistical analysis plan. Although not
prospectively controlled for multiplicity, the FDA notes that the choice of endpoints and analytical approach is consistent with that which would have been anticipated should an analytical hierarchy had been in place and that the prespecified elements were respected.

It is important to note that there are design and analysis limitations in Study 103 as compared to a typical confirmatory phase 3 study design. In particular, because of the staggered dose design and randomization scheme, there's no direct concurrent randomization to the various treatment arms to inform a dose-response analysis or a dose versus placebo comparison based upon concurrent randomization.

However, the placebo arms were pooled across cohorts in compliance with the prespecified statistical analysis plan because of the uneven randomization to placebo in each cohort within the staggered design. The study informed the design of Studies 301 and 302 but also included similar elements as these studies, including the
requirements of a positive amyloid PET scan and
blinded assessment of clinical endpoints.

In the results of Study 103, the FDA agrees
with the 10-milligram per kilogram fixed dose in
Study 103 is the relevant dose to compare to the
high dose in Study 302 for the reasons that have
been described by the applicant. Aducanumab
resulted in a dose-dependent, statistically
significant reduction in clinical decline in the
10-milligram per kilogram fixed dose group as
measured by the CDR-SB and MMSE in comparison with
placebo at month 12.

The clinical efficacy results of Study 103
were supported by a statistically significant
dose-dependent reduction in brain amyloid plaque as
measured by PET in comparison with placebo at
month 12, with a maximum reduction in the
10-milligram per kilogram fixed-dose group as
compared to placebo. The magnitude of the
reduction in brain amyloid plaques in the
10-milligram per kilogram group as compared to
placebo in Study 103 was extraordinarily similar to
that observed in the aducanumab high-dose group in Study 302.

Because Study 103 was designed as a safety and tolerability study, the following must be considered when interpreting the clinical efficacy results. Although there was a statistical analysis plan for analysis of clinical endpoints, there was no control for multiplicity. The placebo group was pulled across the different arms enrolled in the study and is therefore not entirely contemporaneous with the 10-milligram per kilogram treatment arm, and the analysis does not reflect the randomization.

The statistical significance of the 10-milligram per kilogram treatment arm demonstrated with both ANCOVA and MMRM analyses was not robust to the exclusion of post-baseline starting of Alzheimer's disease medications or exclusion of the titration placebo arm. Despite the smaller sample size, the 10-milligram per kilogram dose arm was able to achieve nominal statistical significance according to the
prespecified analysis plan. Also, the
dose-response relationships for A-beta reduction
provides support for the positive finding in the
10-milligram per kilogram treatment arm and are
consistent with the dose-response relationship
observed for CDR-SB and MMSE.

Study 302 provides the primary evidence of
effectiveness of aducanumab. The effect of
aducanumab in Study 302 is robust and exceptionally
persuasive on several of the instruments used to
evaluate efficacy. In fact, the effects observed
for the primary and secondary endpoints encompass
two acceptable approaches to establish
effectiveness, the primary endpoint of CDR-SB that
was prespecified and more traditional approaches in
co-primary endpoints of the ADAS-Cog13 and the
ADCS-ADL-MCI. These results were notably positive.

The estimate of the treatment effect in the
low-dose arm was numerically favorable and was
consistent with the dose-response relationship.
The treatment effects of the high-dose arm is
supported by consistently favorable results across
subgroups of interest. Biomarker results
demonstrate target engagement and treatment effects
on markers of Alzheimer's disease pathophysiology.

The results of Study 103 are appropriately
reviewed as supportive evidence of the
effectiveness of aducanumab. Despite the
limitations of a trial designed to assess the
safety and tolerability rather than effectiveness,
the 10-milligram per kilogram dose arm was able to
achieve statistical significance according to the
prespecified analysis plan.

Also, the dose-response relationship for
A-beta reduction provide support for the positive
finding in the 10-milligram per kilogram treatment
arm and is consistent with the dose-response
relationship observed for both CDR-SB and MMSE.

Study 301 is a negative study and does not
contribute to the evidence of effectiveness of
aducanumab. The results presented in support of
understanding the relationship of Studies 301 and
302 should not be interpreted as explaining why
Study 301 was negative. These analyses are
exploratory by design but limited in scope and
focused on predefined areas of interest.

The rapid progressor analysis indicated that
a small imbalance in the number of rapid
progression patients in the high-dose arm in
Study 301 had a disproportionate impact on the
estimate of the treatment effect using the primary
analysis method.

An examination of dosing in Study 301
indicates that patients with higher exposure to the
10 milligram dose in Study 301 had similar
responses to patients in Study 302. These two
factors contribute to the overall understanding of
Study 301 and together do not meaningfully detract
from the persuasiveness of Study 302.

Substantial evidence of effectiveness is
required for approval. There is a need to
substantiate any individual finding to avoid
reliance on erroneous conclusions, so in general,
two independent studies are typically provided to
meet this need. An alternative approach can be
acceptable. Reliance on only a single study, a
single adequate and well-controlled efficacy study, to establish substantial evidence of effectiveness is a possibility in certain circumstances, particularly when the disease in question is a serious and life-threatening condition and the effect is an important one to the disease.

This approach can be used when the evidence from that single study is quite strong. Examples of the typical characteristics of a single adequate and well-controlled study that might make the study adequate support for an effectiveness claim include characteristics such as a large multicenter study; consistency across study subsets; multiple studies existing within a single study; multiple endpoints involving different events; and a very persuasive finding. Such characteristics serve to increase the reliability of the reported findings and might allow the results of the single study to provide substantial evidence of effectiveness.

Now, thinking of those characteristics and with all things being equal, Study 302 would appear to be a shining example of a compelling single
study, but all things may not be equal. We have an unusual situation. We have one primary study, we have support from a smaller study, futility was declared, and we have a failed sister study.

Each of those things deserves consideration.

I didn't list them in any particular order. The premature termination of the studies required attention. As I have discussed, we brought innovative thinking to this unusual situation, again, compelled to do so by the results staring us in the face regarding 302. When considered on its own, Study 302 would appear to be a home run, but we had to sort out the impact of the futility declaration.

We did that, and unbeknownst to us when we did so, we were able to have an advanced start on something that has affected neuroscience studies more severely than any other therapeutic area, interrupted trials that are happening because of COVID. Our neuroscience trials are hard and complex and they are struggling, and we are helping with that with what to do with missing data and
restructuring trials midstream while attempting to preserve their interpretability, and this is recognized at the agency.

An article from June describing a conference at which the impact of COVID was being discussed by Dr. Peter Marks from CBER and Dr. Peter Stein from OND here in the Center for Drugs, for instance, Dr. Mark said that he anticipates that CBER is preparing for product submission supported by trials that will have holes created by the pandemic.

"We will have to be salvaging what we can from phase 3 trials for products where biopsies may not have been able to get done or other data could not be obtained. It ends up being very much a custom shop where you can't just say for all trials if you do X, you can do Y. It will probably mean going trial by trial and seeing what we can salvage. We will be working very cooperatively with sponsors."

Dr. Stein noted that we are working --

DR. FOUNTAIN: Dr. Dunn, I just wanted to
let you know that you're a bit over your time. Of course, it's your meeting. I'm just letting you know to keep track of time because we might have a bit for clarifying questions. Thanks.

DR. DUNN: Sure. I can truncate the remainder.

Dr. Stein noted that we are working on advising sponsors on what kinds of sensitivity analyses sponsors should consider in managing the situation. He says, "But all I can say at the end of the day, we certainly recognize the impacts. We can't change our substantial evidence standard, but we can be sensible and flexible about how it is applied to kinds of information we're looking at and try to be as sensible as possible. We don't want to see drugs that are potentially very effective delayed."

Dr. Stein pointed out that the Office of New Drugs is committed to helping sponsors overcome the challenges caused by COVID-19. "We will be working very cooperatively with sponsors, assessing what kind of analysis can be done to make sure that the
data can be put together in a way that is convincing and persuasive and lets us get to an approval decision where appropriate."

We rigorously assessed the impact of the early termination and determined that it is not an issue. The data represent accurately the effects of aducanumab in the two trials. With that established, it appears obvious that 302 is independently extremely persuasive.

I am going to pause for a moment just to skip ahead with a few comments to save time, Dr. Fountain. Just give me one second. I've already discussed the breadth of outcomes on Study 302 and the support of data from 301.

DR. FOUNTAIN: And maybe just while you're doing that, I might ask the panel members that we ended the last clarifying question session with Drs. Gold; Perlmutter; Duda; and Kryscio left with her hand up.

If you'd like to ask a clarifying question after now, you can put your hand up, and we'll start with you, but we'll only have a few minutes
for clarifying questions, so if you could please
ask them very brief and to the point.

DR. DUNN: Just quickly, Dr. Fountain.

It's obvious to see why it was critical to
work to understand the failed study as fully as
possible. It's completely consistent with our
guidance. Our guidance says this is what you're
supposed to do. From our long-standing evidence of
effectiveness guidance, which says that because of
the inherent vulnerabilities involved in reliance
on a single study, it is critical that the
possibility of an incorrect outcome be considered
and let all the available data be examined for
their potential to either support or undercut
reliance on a single trial.

Support or undercut. What does 301 do to
302? We have chosen to be conservative and
consider only the latter, the undercut. There are
patterns in the data that given the failed nature
of the trial, our analyses are limited to
explorations. From our more recent effectiveness
guidance, findings from other trials that are not
consistent with the findings of the single positive trial would need to be considered collectively and could weaken the overall strength of evidence; again, explicit instruction to consider the inconsistent findings.

And note the pearl. There could be more than one inconsistent trial. They need to be considered and explored. Our guidance says a failed trial may detract from a positive trial. It seems self-evident that if a failed trial may, but not must, detract, then it follows that understanding the failed trial is a necessary exercise.

Indeed, that is part of the flexibility that our regulations specify for the development of drugs intended to treat life-threatening a severely debilitating illnesses. While the statutory standards of safety and effectiveness apply to all drugs, the many kinds of drugs that are subject to them and the wide range of uses for these drugs demand flexibility in applying these standards. The Food and Drug Administration has determined
that it is appropriate to exercise the broadest flexibility in applying the statutory standards for these conditions.

Dr. Fountain, I'll go ahead and halt there. I only have a few more comments, and most of them are going to reiterating points that we've already made.

Clarifying Questions to FDA

DR. FOUNTAIN: Okay. I'll start with Dr. Gold. And once again, we only have about 10 minutes here to ask questions, and I'd like to get through at least three of them. So maybe ask your question where it can get answered in two minutes.

DR. GOLD: I will try to do this very quickly. It's a two-part question, so one is directed at Biogen in the sense of in their planning of their -- well, actually, let me reverse it. Let me ask about the 103 study.

The effect size of [indiscernible] -- the amount of actual amyloid reduction in the 103 was apparently much larger than in 302, and the difference between amyloid reduction at the top
dose between 301 and 302 appears to be really, really small. It would be helpful to try to understand how with that pattern of data one can view 103 being supportive of 302 and how one can actually argue that a miniscule difference between 301 and 302 can explain such a whopping difference in efficacy.

So I'll posit that one. If I have a chance to go back to the first question, I'd like to go back to that one, too, please.

DR. HAEBERLEIN: Thank you. The amyloid PET reduction at 10 milligram --

DR. FOUNTAIN: I'm sorry. Let me interrupt you there. I thought your question was for the FDA's response to that. This clarifying question is for the FDA. I'm sorry I didn't make that clear.

DR. GOLD: Oh, well --

(Crosstalk.)

DR. FOUNTAIN: We'll have a chance later to ask, but if you want to direct that to the FDA to respond to that --
DR. GOLD: I'm fine to direct it to the FDA because as I understood Dr. Dunn, he believes that 103 is supportive of 302, so the question applies to the FDA, too.

DR. DUNN: Sure. I suspect you're probably going to get a similar answer from my other side.

Dr. Krudys, would you take that? I had a little trouble understanding him, but I think I have the answer. I think Dr. Gold asserted that 103 had a much larger amyloid effect than 302.

Did you hear that also?

(No response.)

DR. DUNN: Dr. Krudys?

(No response.)

DR. DUNN: He might be having some technical problems.

Dr. Gold, I was having a little trouble hearing you. Did you assert that the amyloid effect was much larger in 103 than in 302?

DR. GOLD: Yes. You had a reduction of 1.1 SUVR in 103 and only 0.27 SUVR reductions in 302. So the numbers that I have suggest that it
was much larger in 103 than in 302.

    DR. DUNN: I don't have those numbers at my fingertips right here. I know Dr. Krudys does. I don't believe that's the case. I believe we had very similar amyloid reductions at the 10-milligram per kilogram dose between Study 103, and I think they were precisely the same by my recollection.

    DR. GOLD: Okay.

    DR. DUNN: In terms of your other question, I don't think that there's any suggestion that the -- the difference in reduction in amyloid between 301 and 302 is notable and reflects, rather obviously reflects, a diminished exposure compared to 302, but I don't think the link that you drew there, which is that everything is necessary attributable to that, is necessarily the case. But I think that the numbers are rather precise.

    It is notable that the amyloid effect is lower. I think you see evidence in other factors -- again, small numbers, exploratory analysis, but you see some of the downstream effects also being diminished. So there's an
overall pattern of diminution of response. But again, I don't have those data. Dr. Krudys has those data, and I want to make sure we check with him if he's available.

DR. GOLD: Okay.

(Crosstalk.)

DR. FOUNTAIN: Let me ask it a different way.

Dr. Gold, does that answer the nature of your question?

DR. GOLD: It does. Do I have permission -- can I ask one more or do we need to move on?

DR. FOUNTAIN: I think we'll need to move on.

DR. GOLD: Okay.

DR. FOUNTAIN: But hopefully, we'll regain some time to ask some follow-up questions later.

Dr. Perlmutter, do you have a question for the FDA rather than for the sponsor?

DR. PERLMUTTER: It's for the sponsor. It could be answered by either one, actually, two
related questions.

One is, in 301, if the high-dose response -- the lack of response was due to a lower dose, but yet the lower dose in 301 provided benefit. Was the lower dose in a high dose lower than the lower dose? Does that fit on the dose-response curve?

Then the second part of my question is if we're using the PET A-beta measurements as a biomarker of efficacy, wasn't there a lack of correlation between the response in the PET findings with the CDR-SB, and how do you explain that if that biomarker is relevant for their clinical benefit?

DR. DUNN: This is Dr. Dunn. I can speak to the second one. We're not using the amyloid as a surrogate for efficacy.

Dr. Krudys, are you online now?

DR. KRUDYS: Yes, I'm here. Can you hear me?

DR. DUNN: Yes.

DR. KRUDYS: Can you hear me?
DR. DUNN: Yes.

DR. FOUNTAIN: Yes, we can hear you.

DR. KRUDYS: Okay. Thank you. I'm sorry.

Kevin Krudys here. I think there's a point about there is a population of patients in Study 301 that I have in my presentation that we don't have an explanation for. So they did have some exposure consistent with about a dose of 6, yet they don't show the response that we see in Study 302.

So there is a small subset of the population 301 that is not consistent with what we would expect from a dose-response relationship. But from what we've seen in Studies 103 and 302, we do see that if you increase the concentration of the exposure, you're more likely to see a response. So therefore, we look at the results in the high dose of Study 301, and you see the patients who had the highest exposure have a response that is similar to that in Study 302.

I think if we didn't see that, it would call to question the results that we saw in Study 302,
but we're seeing a consistent response at the highest exposure. But there is, like I said, a subset of patients who are in between first of their exposure and don't have the response as we would project based on the exposure-response relationship we're seeing in Study 302.

DR. PERLMUTTER: Thank you for that. But as a follow-up for that, if you tried to remove or if you removed rapid progressors from the analysis in 301 and then you find it changed, how do you do that prospectively? Isn't that always for the treatment, is follow up how much they've changed? How would that even be implemented?

DR. FOUNTAIN: Well, maybe we can save that for discussion because that would be something rather than for what we've already done, but sort of for the future.

Can we save that for the discussion session?

DR. PERLMUTTER: Okay. Thank you.

DR. FOUNTAIN: Okay.

Dr. Kryscio, I see you've put your hand down, so I'm assuming there's not a question. And
we have time for one more question in this session, and I believe next in order would be Dr. Emerson.

DR. EMERSON: Thank you. Dr. Dunn --

DR. FOUNTAIN: Do you have a brief one, please?

DR. EMERSON: I have. Well, I just want to make one comment of course, is that the advisory committee is meant to see whether the FDA opinions are advisable, so of course we're not just to be a rubber stamp for the FDA at all, and that futility rules in general help public health immensely; although I will concede that the particular futility rule specified for this study was ill-advised, more because how it was so liberal in futility.

But you remarked that the assumption of a common treatment effect was violated in the futility rule. If that's the case, how will you distinguish between the population that was in 302 and therefore has a treatment effect and the population in 301 that apparently does not have a treatment effect?
I'll note that the futility analysis presumed that there would be differences in the estimated treatment effect, and that is why presumably they chose to use the combined groups to try to get a better estimate. So your statement that the treatment effects common between the two groups is violated argues that we should not write an indication that encompasses both study populations.

DR. DUNN: What indication are you referring to, sir, that you're describing as encompassing both study populations?

DR. EMERSON: Again, if you are saying that the futility analysis was wrong because there was an assumption of a common treatment effect for both studies and that that was violated, that must mean that your belief that the treatment works in the 302 population but doesn't necessarily work in the 301 population must be somehow taken into account as you write an indication for this drug. How will you do that?

DR. DUNN: Yes. I think that the point that
we were making -- and again, I'll invite others to comment on it. I think you're certainly aware that I'm not a statistician. The point that I'm making is that the futility analysis -- as our understanding from the sponsor, so perhaps maybe Dr. Mallinckrodt would comment on this -- was predicated on an assumption that the treatment effects would be similar and that they were not.

So the futility analysis was conducted and executed according to its prespecified plan, but an assumption on which it was based didn't hold. That's the extent of what I understood to be true.

DR. EMERSON: So the FDA statistician, who we haven't heard from in this meeting but who did write a very nice report, might also bring to bear on this about what the distinction is between a treatment effect common between the two studies and similar estimates of treatment effect between the two studies and the difference between those. Which of those were assumed in the futility rule and which of those need to be assumed for issuing the general indication for all patients?
(No response.)

DR. EMERSON: Did I lose anything? There is not response coming?

DR. MASSIE: Hi. This is Tristan. Can you hear me --

DR. EMERSON: Now, I can. Thanks.

DR. MASSIE: -- the FDA a statistician.

DR. FOUNTAIN: Yes, we can hear you. Thank you for weighing in.

DR. MASSIE: Thank you. I'm not sure at the interim analysis that the treatment effects were different at an interaction formal level. Maybe the sponsor could inform us about that.

DR. EMERSON: Again, my question is -- and I'd be interested in your opinion -- in terms of using conditional power, which I think is a poor choice for a variety of reasons just because of understanding the futility rule. But in using conditional power, my presumption would be the motivation for combining the treatment estimates across the two studies would be to get a more stable estimate to use in the conditional power
calculation under the assumption that there would be differences in the estimate, but they were estimating the same treatment effect. It is a major scientific question if you are presuming that there is a different treatment effect, the true treatment effect between these two studies.

Is my reasoning in agreement with what you would say?

DR. MASSIE: Yes. I think, a priori, it makes sense to have a more stable estimate when you have two identically designed studies and you're at 50 percent in both. So if they're identically designed, if you combine them to get a more stable estimate, that makes a lot of sense.

DR. FOUNTAIN: So I think that's the answer. And maybe we could circle back on the significance of that answer later when we discuss the significance only because I'm afraid we'll, I think, go over a lot more time.

Is that acceptable to you, Dr. Emerson?

Does that essentially answer the specific question?

DR. EMERSON: Yes. Thanks.
DR. FOUNTAIN: Thank you.

Alright. That ends the clarifying questions for the FDA. We'll now break for lunch. We will reconvene in one hour, a little less than one hour, 55 minutes, at 1:30 p.m. Eastern time. Panel members, please remember that there should be no chatting or discussion of the meeting topics with other panel members during the lunch break. Additionally, you should plan to rejoin at around 1:15 to ensure you're connected before we reconvene at 1:30. And just as another parenthetical note, of course you can remain on the Adobe Connect as well.

So we'll reconvene at 1:30 Eastern time.

Thank you.

(Whereupon, 12:36 p.m., a lunch recess was taken.)
AFTERNOON SESSION
(1:32 p.m.)

Open Public Hearing

DR. FOUNTAIN: Welcome back to the meeting. I'm Nathan Fountain, the chair of the meeting. We will now begin the open public hearing session.

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

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

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

The FDA and 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 great 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 me, the chairperson. Thank you for your cooperation.
Each of the open public speakers will have three minutes for their presentations.

Speaker number 1. Will speaker number 1 begin and introduce yourself? Please state your name and any organization you're representing for the record.

MR. BORGOFF: My name is Jeff Borghoff, and I represent the Alzheimer's Association and my clinical trial center at Memory Research Institute of New Jersey. I have no conflict of interest with regard to the statement that you made. Thank you for allowing me to speak to you today about my personal experience with the Biogen aducanumab clinical trial. This experience, however, is not limited to me. It extends to my wife, my three children, and all that know and love me.

When I was first diagnosed with Alzheimer's disease in 2016 at the age of 51, I quickly resolved myself to the prognosis of the disease and immediately took steps to confront this monster and enrolled in the aducanumab trial. I understand that Biogen needed to make a decision to halt the
trial based on a futility analysis, however, it is
difficult to express my overwhelming sense of
gratitude that in October of 2019, the same year,
we were notified the trial was going to be reopened
for reenrollment as the EMBARK study with a goal to
move forward to FDA approvable.

    During my time in the trial, my cognition
and other neurological functions have not
significantly declined. For that matter, we
believe there has been some improvement. In
October of this year, I completed my ninth EMBARK
infusion and I'm still doing and testing well
without any known side effects. It's important for
this committee to understand that my family and I
know aducanumab is not a cure for Alzheimer's
disease. We understand that it is meant to slow
the decline of neurological functions, and that is
our hope.

    My wife and family often say that we can
live with the damage that has been done to my brain
from Alzheimer's as long as I can live longer. In
many cases with the diagnosis of younger onset of
Alzheimer's disease, the person is face was just a few years. I'm coming up on my fifth year with my three kids graduating from a university and celebrating my middle daughter's quality-of-life milestones and bucket-list items we thought we would miss. We believe that grandchildren will be the next milestone bucket-list items and no small part to the much needed aducanumab medication.

My wife Kim has said, "Without this medication, I do not believe Jeff would have been mentally present and able to participate in our middle daughter's wedding." My daughter Aubrey [ph] stated, "It has meant the world to me. It's a once-in-a-lifetime opportunity that we have been blessed with." And my daughter Erin [ph] has said, "I believe this medication has given me the opportunity to have my dad longer as we once knew him."

My request is that you allow the aducanumab clinical trial to continue with the hope of its approval. Thank you for your time and consideration. That completes my statement.
DR. FOUNTAIN: Thank you.

MR. BORGHOFF: I would like to say, though, that in the background was some papers. That was very distracting.

DR. FOUNTAIN: Yes. Everyone who's not speaking, if you'd please put your phone on mute. That would be helpful, including all the panelists and committee members.

Speaker number 2, your audio is connected now. Will speaker number 2 begin and introduce yourself? And please state your name and any organization you're representing for the record. Thank you.

DR. CAROME: I'm Dr. Carome, director of Public Citizen's Health Research Group. I have no conflict of interest. Public Citizen strongly opposes FDA approval of aducanumab for the treatment of Alzheimer's disease because the Pivotal 3 trials ENGAGE and EMERGE, plus the phase 1 Study 103, failed to provide substantial evidence of effectiveness.

The pivotal trials were terminated early
after the prespecified interim analysis for
futility and showed only EMERGE was turning
positive, whereas ENGAGE was unlikely to meet its
primary endpoint. A subsequent post hoc analysis
of the trials showed that in EMERGE, high-dose
aducanumab followed improvement in the primary
efficacy endpoints, but in ENGAGE, no benefit with
low- or high-dose aducanumab. Such post hoc
analyses are highly susceptible to bias, do not
provide substantial evidence of effectiveness, and
should only be used to generate hypotheses for
possible future trials.

We agree with the following assessment by
Dr. Knopman, a Mayo Clinic neurologist and member
of this committee who is recused today because he
was a site investigator for ENGAGE, quote, "The
evidence that aducanumab has any benefit in persons
with Alzheimer's disease is terribly weak."

Contrary to FDA's assertion, the EMERGE and
ENGAGE data also must be assessed in the context of
the two-decade history of 22 other failed drugs
targeting amyloid-beta accumulation, including five
other anti amyloid-beta monoclonal antibodies, many of which caused harm. See this table. In this historical context, which called into question the amyloid hypothesis, there is a significant probability that the EMERGE efficacy results represent a false positive.

FDA's statistical reviewer Tristian Massie correctly highlighted the lack of substantial evidence of effectiveness for aducanumab. In this case, we do not have a single strong study in isolation. On the contrary, we actually have a second trial in which the purported effective dose was in the wrong direction compared to placebo. Under the null, if winning in just one study out of two was enough, then there's a chance that falsely rejecting the null would be 0.0975 across the two studies. Furthermore, if we select only the better study, our estimate is very likely biased and we already know not consistently repeatable. Thus, excluding data from a large trial without sufficient justification is unscientific, statistically inappropriate, and misleading.
My last slide. In closing, FDA must demand another premarket, randomized, placebo-controlled trial of aducanumab. FDA approval of the drug would further damage the agency's already diminished credibility. We therefore urge the committee to vote no on question 7 and recommend that FDA not approve this drug. Thank you.

DR. FOUNTAIN: Thank you.

Speaker number 3, your audio is connected now. Will speaker number 3 begin and introduce yourself and the organization you're representing for the record?

MS. TAYLOR: My name is Geri Taylor.

MR. TAYLOR: And my name is Jim Taylor.

Geri and I have twice spoken to Biogen employees. We were paid several hundred dollars, funds subsequently donated to Alzheimer's research. With her nursing experience, Geri is a trained observer. With her research background, in the 1970s, she co-authored the very first article on the importance of medical second opinions in the New England Journal of Medicine. As the COO of the
largest long-term care health facility in New York City, Geri oversaw dementia and hospice facilities. As an ApoE double-4 carrier, she has witnessed the impact of Alzheimer's on both parents.

Eight years ago, Geri was diagnosed with MCI, and since we have spoken to over 10,000 people. We speak to confront the stigma of dementia, to encourage living with joy and passion during the many high functioning years prior to late stage, and to strongly encourage participation in clinical trials.

Geri participated in Study 103 at the 10-milligram dosage for over four years. Ironically, on the day that the trials were terminated, I was in Bethesda, Maryland serving as the patient representative at an FDA Alzheimer's public hearing. Being ineligible to serve today because of Jerry's trial participation, I well remember the preparation time and challenging deliberations required. Geri and I thank each of you for your participation today.

Aducanumab's termination was especially
difficult because we believe that Geri
significantly benefited. Her cognitive decline was
extremely slow for over four years and we
functioned very much as equals in our busy life as
advocates. Only six months after the trial's
termination Geri's decline rapidly accelerated.
She now experiences challenges with halting
communication and impaired cognition, but she sits
beside me and now joins in these comments.

Anecdotal, of course, but we believe
representative of those Study 302 participants on
10-milligram dosage for 18 months, whom we know
experienced significant slowing and cognitive and
functional decline. Even if only some individuals
respond to treatment, aducanumab will be a
tremendous ray of hope for those who today, with no
meaningful disease-modifying therapy, live
difficult lives. Geri joins me in urging you to
approve aducanumab. Thank you.

MS. TAYLOR: Yes, thank you.

DR. FOUNTAIN: Thank you.

Speaker number 4? Speaker number 4 is now
connected, and will speaker number 4 begin and
introduce yourself? Please state your name and any
organization you're representing for the record.

MS. BONHAM: Good afternoon. I have no
conflict of interest. My name is Kim Bonham and my
husband Kevin, who is here with me, was diagnosed
with early onset Alzheimer's in October of 2016 at
the age of 58. Our daughter Kaia [ph] was 9 years
old at the time. I have been an occupational
therapist for the past 33 years, and I knew we
needed to find answers when Kevin began having
difficulty with his memory and visual perceptual
skills.

Unfortunately, after six months of doctors'
appointments and multiple diagnostic tests, we
received the most devastating news, early onset
Alzheimer's. Thankfully Kevin's doctor recommended
the Biogen clinical trial and we were blessed that
Kevin qualified and was enrolled in the ENGAGE
study immediately.

In January of 2017, he received his first
aducanumab infusion. He responded beautifully for
the two years that he participated in the study. We later found out that he had been fortunate enough to have received the 10-milligram dose. During that time, he remained stable and was able to continue working at a local utility company where he had been making maps for the past 40 years. He was able to manage all of our finances, complete household projects, and navigate through his computer programs without difficulty. His reading skills and concentration was improving. He was so excited that he could tell time once again on his analog watch. This was a skill that he had lost and now regained.

Unfortunately, that all came to a halt when the trial ended in March of 2019. All of the progress that he had made over the course of two years has been slowly stripped away from him in just eight months. Month by month, he had declined to the point where he had to go on disability in November of 2019 because he could no longer perform his job duties.

Kevin began to have significant deficits in
executive functioning such as planning, organizing, and following through on tasks. He was also having difficulties with visual processing, memory, and his sense of time. This was so hard on our family, and we were feeling overwhelmed, so you can only imagine how elated we were when we learned that Kevin could resume receiving the aducanumab infusions in the EMBARK study.

He has received 5 infusions to date and is being titrated to the 10-milligram dose. We are incredibly grateful for this opportunity to speak with you today. Kevin has already started to see improvements in his mental clarity, and our daughter Kaia has been able to bike, and hike, and walk our dogs with her dad.

We are asking you from the bottom of our hearts to consider bringing aducanumab to market. We know firsthand that it was helping Kevin and we don't ever want to be in the position again where we do not have access to this very effective treatment. We want others facing this horrific disease to have access to this promising therapy.
and to have hope once again as we do. Thank you.

DR. FOUNTAIN: Thank you.

Speaker number 5, your audio is connected.

Will speaker a number 5 begin and introduce
yourself? Please state your name and any
organization you're representing for the record.

DR. PIKE: Hello. I'm Dr. Joanne Pike,
chief strategy officer of the Alzheimer's
Association. On behalf of all those living with
Alzheimer's disease, their caregivers, and their
families, thank you for the opportunity to address
the committee. For decades, millions of Americans
and their loved ones have waited for access to a
therapy that addresses the underlying disease, not
just the symptoms, as they face the devastating
reality of this relentless disease.

As a leading voluntary health organization
in Alzheimer's care, support, and research, each
year we speak with hundreds of thousands of
families through our 24/7-365 help line and serve
hundreds of thousands more, providing access and
direct support to people living with this disease
and their families and communities across America. Through our work, we see firsthand, every day, the devastating toll Alzheimer's disease takes on individuals, their caregivers, and families.

The trajectory of cognitive and functional decline is currently inevitable. The disease is fatal. For individuals living with Alzheimer's, they lose more and more as it progresses. It is not just memory. They lose the ability to participate, they lose their independence, they lose themselves.

For families and friends watching a once vibrant, curious, and articulate loved one slip away is heart-wrenching. On top of the emotional pain, they become caregivers. They take on overwhelming tasks and they do so at great personal expense to their physical health, their economic security, and their emotional well-being.

That is why the decision before the members of this committee is so critical. The need for relief for millions of Americans impacted each day by the crushing realities of Alzheimer's is
overwhelming. Given the devastating toll of this
disease, the publicly released data justify
approval accompanied by a face for postmarketing
surveillance study. Requiring completion of an
additional phase 3 trial would deny access up to
four years while it is completed. A four-year
delay is too long for too many. The potential to
delay decline would be denied to millions and the
potential to say damage and death for some
caregivers is real.

In the time lost for spouses, partners,
moms, dads, grandmothers, grandfathers, and uncles,
and friends and neighbors cannot be recovered. We
urge approval. We acknowledge that trial data has
led to some uncertainty among the scientific
community, so we ask you to weigh this against the
certainty of what this disease will do to millions
of Americans absent a treatment. We are grateful
for the advisory committee and FDA's careful
consideration of all evidence and information.
Thank you for the opportunity to comment.

DR. FOUNTAIN: Thank you.
DR. ZUCKERMAN: Thanks. I'm Dr. Diana Zuckerman, president of the National Center for Health research. Our center is a nonprofit think tank that scrutinizes the safety and effectiveness of medical products and we don't accept funding from companies that make those products. My expertise is based on my postdoctoral training and epidemiology in public health and previously as a faculty member and researcher at Vassar, Yale, and Harvard. I've also worked at HHS, the U.S. Congress, and the White House, and I'm on the board of the Alliance for a Stronger FDA, which lobbies for more appropriations for the FDA.

We've all seen the devastating impact of Alzheimer's disease, and those of us whose loved ones have suffered desperately we want to help them; and ourselves, we want to avoid that fate. I'm going to talk about what we've learned about the two studies using quotes from FDA's slides for today.

As everyone knows, Study 302 was positive with the high-dose treatment and Study 301 was
negative and actually favored placebo. Blinding is always very important in a randomized double-blind study, and since a large number of patients, almost half, had ARIA, I want to just mention, although there was a mitigation where raters were independent of patient care and so remain blinded, the patient's weren't blinded. They certainly, many of them, would have been suspicious because they were treated differently to manage these side effects.

Most of you know that post hoc analyses are not considered scientifically appropriate, but given the desperate need to find a treatment for Alzheimer's, I actually have no argument with analyzing the hell out of the data in an effort to find out if the drug is effective for some patients under some conditions.

Nevertheless, I completely agree with FDA's statistical concerns that were expressed in Dr. Massie's slides. Inconsistency, they wrote that, "We have a equally sized and identically designed Study 301 that directly contradicts 302,
and the 301 high dose is numerically worse than placebo," and then there are concerns about the null hypothesis.

Here are other quotes from the FDA slide.

"If you have two studies and you take the best and pretend like it's the only one, their estimate is likely biased." Another quote, "At best, evidence is from 302 only and there exists conflicting, adequate, well-controlled evidence."

DR. FOUNTAIN: Is this the last slide?

DR. ZUCKERMAN: Almost. I've got --

DR. FOUNTAIN: I want to make sure we have time for everything.

DR. ZUCKERMAN: Sure.

The impact on the ongoing and future trials for other promising Alzheimer's drugs is really important. It's going to create recruitment challenges for ongoing trials if this product goes on the market.

So you have a really tough decision today because there's an urgent desperate need for treatment, but the family dilemmas are going to be
that this treatment, if approved, is going to be extremely expensive, and it will not be clear who it might work for, so some families will really lose all their savings in order to hope that the treatment works for them.

Most important, if we can't get long-term data once it's approved, which is usually what happens, that's really a problem. Although the study was terminated early, and that does not seem to affect the efficacy, we don't have that information and we certainly don't have a --

DR. FOUNTAIN: Okay.

(Crosstalk.)

DR. ZUCKERMAN: Thank you very much.

DR. FOUNTAIN: Yes, thank you for your comments.

Speaker number 7, your audio --

MR. VRADENBURG: My name is George Vradenburg. I'm sorry.

DR. FOUNTAIN: No, go ahead.

MR. VRADENBURG: My name is George Vradenburg, chairman of UsAgainstAlzheimers, a
patient-led nonprofit with the single mission to stop Alzheimer's. We're supported in that mission by thousands of individuals and scores of companies, including Biogen.

I joined this battle against Alzheimer's because my family has experienced three generations of Alzheimer's over 40 years. At this pace, my children and potentially my grandchildren, are in the Alzheimer's bullseye, but mine is just one family among tens of millions of American families who are and will be touched by this disease. I speak today in support of all those families.

What matters to us? We know from our own statistically rigorous studies what matters most, that all 10 of the things that matter most to those early in the Alzheimer's journey are embodied in the clinical endpoints in the aducanumab trial. But for us, for example, and ADL scale is not just an endpoint, it's more weeks and months and maybe years of living independently; of being safe when left alone; of being able to use the shower or the toilet.
To get to the best-in-class drug, a cure, we must have a first-in-class drug because we have learned. With so many other challenging diseases, all of us who have been through cancer know there's no sure thing and side effects can be brutal. But those of us with early Alzheimer's aren't afraid of headaches for goodness sake; we're on the path to dying.

A statistician might speculate there's a 38 percent chance that aducanumab doesn't work as advertised, so delay approval for yet another study. But that means that even for skeptics there's a 62 percent chance that it does work as advertised, and if we wait for another study, there's a zero percent chance that people will benefit. A 62 percent chance of benefit to zero, we'll take those odds now.

For us, waiting for perfection is not an option. We're losing the ability to recognize our family members now. We're becoming agitated now. We are losing ourselves now. We simply can't wait. The signal you send today will have a ripple effect
far beyond this one drug. The signal you send
today can stop the path to a cure for years or
correct the sound of the starting gun on
innovation.

    With approval, as sure as day follows night,
drugs 2, 3, and 4 will follow faster. With
disapproval, our community will continue not to
think about brain health, believing based on a
negative vote that nothing can be done to stop
cognitive decline.

    With approval, our community will know
Alzheimer's enemy has been finally engaged. We'll
know that science and time are now on our side. We
will engage with our physicians to learn with early
detection what can be done to slow this disease.
Action will replace denial. Hope will replace
despair. I urge you to vote for hope over despair.
I urge you to recommend approval of aducanumab.

Thank you.

    DR. FOUNTAIN: Thank you.

Speaker number 8 is connected to the audio.

You may begin.
MS. COMER: My name is Meryl Comer. I'm a long time caregiver and founding board member of the nonprofit, UsAgainstAlzheimer's. I have no conflict of interest. I come before you today to ask you to support the approval of aducanumab.

This distinguished panel understands the mechanisms of Alzheimer's disease, and I know your responsibility is to weigh carefully the clinical benefit of a new therapy. But I have lived deep inside the cruel labyrinth of this disease 24/7 for more than two decades, personally caring from my husband and my 85-year-old mother in our home.

The diagnosis of Alzheimer's is often late. Smart people hide out and predictions about disease longevity are often inaccurate. My husband, a physician and former chief of hematology-oncology at NIH, was misdiagnosed for four years while we were held hostage by bouts of paranoia, hallucinations, and aggressive behaviors uncharacteristic of his personality. He had maintained his brain and it just didn't matter.

When he was finally diagnosed, we were told
he would not last five years. His disease was early onset. By then he had already forgotten who I was, other than a safe space, shadowed me for cues and comfort, and had no insight about his prognosis. Traumatic episodes were followed by long plateaus as he sunk deeper into the disease. I buried my husband this February, 24 years later.

Now Alzheimer's is coming for me and the generation of 56 million baby boomers, the oldest of whom will start turning 75 at the rate of 10,000 a day in 2021. It should also not be lost on this panel that two-thirds of Alzheimer's victims are women. Today a diagnosis of mild cognitive impairment is still an uncertain and frightening journey. The prognosis is numbing.

So I ask the committee, what is time worth when you're tethered to a diagnosis where you slowly lose your intellect, independence, and the very essence of who you are as an individual? Those who are eligible must be given the chance to buy time. Let them work with their physicians to decide if the risk is worth its potential.
The unmet need is obvious. Please take every measure to bring this therapy forward. We don't expect guarantees. All we ask is the chance for more time upfront and ahead of our fate. That for millions of patients and their families is clinically meaningful. Thank you for your time.

DR. FOUNTAIN: Thank you.

Speaker number 9, your audio is connected now, and you may begin.

MR. O'BRIEN: Yes, I will read from this. My name is Greg O'Brien. In the interest of full disclosure, I'm a board member of UsAgainstAlzheimer's, an organization that receives donations and program support for Biogen and others. I'd like to speak in support of Biogen's drug from a perspective of someone living with Alzheimer's.

The disease took my maternal grandfather, my mother, paternal uncle, and before my father's death, he too was diagnosed with dementia. Then it came for me. I was diagnosed about nine years ago with early Alzheimer's after experiencing the
horrific trademark symptoms, and after two serious head traumas, the doctor said I mask the disease in the making. I also carry the Alzheimer's gene ApoE4. I'm 70 now.

As you know, Alzheimer's is a disease that can take 20 or more years to run its demonic course. I know the front line well. As a career journalist, I wrote about my journey in a book called On Pluto: Inside the Mind of Alzheimer's. We have in this country some of the brightest minds in the world, but Alzheimer's has been a Rubik's Cube for which so far there is no winning solution. The best we can do now is to slow the rate of cognitive and functional decline in persons in the earlier stages of Alzheimer's. That's a significant step for them.

Biogen's drug won't help me in my journey now, but for those in the early stages of this disease, it would offer hope where to date there has been no semblance of hope. It offers a chance to preserve independence in the early stage for a longer period. It offers more time to be us, more
time in the moment with our families.

This may not be a victory at last on medical front for those of us on this serpentine journey, but even if it is not a perfect drug for everyone, it's a big step forward that offers more time and real hope to many with this disease. After years of great disappointment and drug trials, for those in the throes of urgency as our minds decline, please offer us some hope. Please recommend approval of this drug therapy.

Sorry I can't properly pronounce the name of the Biogen drug. It's just too complicated for me, but thank you for listening.

DR. FOUNTAIN: Thank you.

Speaker number 10, your audio is connected.

DR. SALLOWAY: Good afternoon. I'm Dr. Stephen Salloway, professor of neurology and psychiatry at Brown Medical School and director of the Memory and Aging program at Butler Hospital. I have 30 years experience as a dementia specialist caring for patients with Alzheimer's disease and I've been the site PI for more than 100 clinical
trials for Alzheimer's.

I was the lead author on the first report of ARIA in 2009 and I'm an expert in ARIA management. I have no significant financial interest with the sponsor or others. I'm speaking on behalf of my patients at this meeting, and I prepared these remarks on my own without consultation with Biogen.

I want to thank the thousands of courageous study participants who contributed to the data under review today. Aducanumab produced a significant dose-dependent lowering of amyloid plaques in all studies and the slowing of cognitive decline in two out of three trials. ARIA when present was typically transient and manageable with careful titration and safety monitoring.

Could I have my slides, please?

I was a site PI for the PRIME and ENGAGE trials and I treated more than 60 patients on aducanumab with many on open treatment for more than five years. We follow our patients closely and I'm well aware of changes in their daily functioning. Overall, patients on open treatment
with aducanumab declined less than expected over a period of years.

Let me give you an example. Here is Neil and Maureen Corkery. Neil, a 78-year-old retired school superintendent, developed memory loss and trouble expressing himself six years ago. Positive amyloid and tau PET scans helped confirm the diagnosis of MCI due to AD, and you can see from his mini-mental state graph that his cognitive performance has remained remarkably stable over five years from monthly infusions of high-dose aducanumab. He only began to decline after aducanumab was stopped in March of '19, but he's doing better, back on aducanumab through the follow-on trial, living at home, thriving and socializing regularly with his friends. His positive response to aducanumab is not isolated.

We are at a critical juncture in Alzheimer's treatment. Too many memories will be lost if we have to wait four to five years to complete a new trial. The positive benefits of aducanumab clearly outweigh the certainty of decline if this treatment...
is not approved. Approval of aducanumab will be associated with many firsts for Alzheimer's: the first drug approved in 17 years; the first approval for MCI due to AD; and the first treatment targeting a core pathology disease.

Approval of aducanumab would provide a treatment foothold we can build on akin to the approval AZT, which despite its limitations energized HIV, leading to powerful new treatments. The hope of preserving the quality of life for thousands of patients like Neil Corkery are waiting eagerly on your decision. Thank you.

DR. FOUNTAIN: Thank you.

Speaker number 11, your audio is now connected. Please introduce yourself and state your name and any organization you're representing for the record.

MR. BRISTOL: Hi. I'm Peter Bristol. I'm representing myself. I have no conflict of interest, and I'm definitely honored to be here today. In my opinion, Biogen's aducanumab should be an Alzheimer's disease therapy.
I'll present my statement based on my experience and will share my passion to see a cure for AD. I have a family history of Alzheimer's disease and dementia and my forgetfulness was limiting my effectiveness at work. After my mother, uncle, and most recently my brother died with AD, I took the initiative to see the preeminent Alzheimer's and dementia researcher, as you heard, Dr. Stephen Salloway at Butler Hospital. I was eligible and joined the A4 study. The A4 study is a phase 3 clinical trial for cognitively normal older adults whose brain scans show evidence of amyloid buildup, which places them at risk for memory loss and cognitive decline associated with Alzheimer's disease. Three motivators, hope, trust, and commitment, helps many other trial participants and helped me persist through the initial four-and-a-half-year trial and my current four-year, open-label extension. Hope, hope that by participating in a trial I will find a cure for AD and maybe even have any of my further cognitive decline slowed or stopped.
Trust, trust that I will be treated safely and respectfully, which I am.

Commitment, commitment to my children and grandchildren and to the effort and time needed to complete the study.

Approval of a therapy using aducanumab will give hope and encouragement to the tens of thousands of current Alzheimer's and dementia trial participants like myself and give confidence to those considering joining a study knowing their help will be recognized and productive in finding a cure. More studies are ongoing and more trial participants are needed to build on the success of aducanumab.

My philosophy is, to climb a mountain you need to take one step at a time. Approving aducanumab is one step closer to finding the cure for Alzheimer's disease. As the Alzheimer's Association states, quote, "The first survivor of Alzheimer's is out there, but we won't get there without you," end quote. Thank you for letting me speak.
DR. FOUNTAIN: Thank you.

Speaker number, 12, your audio is now connected. Please introduce yourself and state your name and any organization you're representing for the record.

MR. PATTERSON: My name is Ed Patterson. I'm representing myself. I am a 73-year-old individual. I live in the central Florida part of the country. I strongly encourage the FDA to approve Biogen treatment for Alzheimer's disease. I had a very successful career in the banking data processing business. I traveled the U.S., Europe, Middle East, Mexico, speaking with presidents and other executives in banks. I often booked my own travel arrangements.

About 10 to 12 years ago, my husband David, a nurse, noticed that I was experiencing cognitive challenges such as double-booking airline flights, duplicating of bill payments, memory issues, concentration issues, and word searching. There were many visits to the doctors and urologists and I participated in several memory tests about nine
years ago. There were challenges with my insurance company paying for MRIs, amyloid and tau PET scans, and spinal taps.

In 2018, after a series of memory testing, I was accepted into a blind drug study as a result of accumulation of amyloid plaque. It was an 18-month blind study. Six months into the study, the drug was pulled by the FDA. At that point I learned I was taking the study drug and it was helpful. I was told I had to wait six months to enter into another study.

I had the opportunity to enter into a second study. As a result of the administrator of the study incorrectly scoring my study, my point was one point higher. I was disqualified. After several additional memory tests, I was asked to participate in a third study. Because of a heart attack between my second and third study, I was disqualified and I have to wait for another year to participate in another study.

I share this journey with you to identify the years that I have passed since initial onset,
testing, and diagnosis. Biogen now has a drug
therapy that has successfully passed clinical
trials and the drug has clear signs that it works
as intended. A therapy of this nature that I and
many others, and my care partners, strongly support
provides an opportunity to slow down my cognitive
decline.

As an individual identifying with
accumulation of amyloid plaque, and I also carry
the gene, I can only wish for a chance to take this
first therapy. Extending my cognitive life and my
cognitive ability, taking care of myself, and not
being an early burden on my care partners is what I
prefer. While other drug approvals are further
down the road and subject to trial results, in
delaying the Biogen therapy, I may not have the
opportunity to participate and extend a good life.

I'm an active advocate and advisor with the
Alzheimer's Association and I want to continue with
that path to provide awareness. I request the FDA
to approve the therapy and to do so quickly for the
benefit of myself and millions of others in the
United States just like me. Thank you for the
opportunity and comments.

DR. FOUNTAIN: Thank you.

Speaker number 13, you're audio is connected
and you may begin.

MR. DWYER: My name is John Dwyer. I am
cofounder and president of the Global Alzheimer's
Platform Foundation, a nonprofit patient advocacy
organization dedicated to speeding clinical trials
and the discovery of therapies for patients
stricken by Alzheimer's disease. Our mission is
funded by many of the world's leading
philanthropies and pharmaceutical companies active
in the AD field, including Biogen.

Over a dozen of my family members are
suffering with or have died from Alzheimer's. I'm
currently assisting with the care of three
individuals who have been diagnosed with mild
cognitive impairment. One person has early onset.
On behalf of the millions of patients whose health
and welfare hang on this body's deliberations, we
urge the committee to recommend the approval of
aducanumab for patients with MCI and mild Alzheimer's disease.

There are several reasons that compel this result. Patients with mild Alzheimer's disease have not been afforded a new approved therapy in over 17 years. It kills more than 500,000 people per year and without making inappropriate comparisons, far exceeds the COVID pandemic's tally that we will experience this year.

It is fair to say that no other disease of Alzheimer's scale and mortality has gone so long without incremental therapeutic relief, and speaking from substantial personal experience caring for my own family, the existing approved drugs offer fleeting or no real relief in addressing the symptoms of mild Alzheimer's disease. Aducanumab is the first breakthrough therapy that offers disease-modifying benefit and exceeds current approved therapies for this group of patients.

Patients with mild cognitive impairment are even more therapeutically orphaned. There is no
approved therapy for patients diagnosed with MCI. Millions of patients receive this devastating diagnosis without access to an FDA-approved therapy tested and measured for fitness for their condition. Approving this drug will offer hope, catalyze advanced blood tests, and encourage diagnosis of the disease earlier and more effectively. And frankly by definition, aducanumab merits approval for MCI. It demonstrated significant effectiveness in treating the condition that afflicts millions of Americans that have no alternative therapy.

Aducanumab delivers real improvements. The therapy slowed decline in six critical clinical aspects of AD patients' lives. More importantly, practically speaking, it offers AD patients the most precious of benefits, more time; more time to love their family, to live their lives, and to not be a burden. There is nothing MCI and mild AD patients and their families value more. Ask anyone who has lost someone to this disease twice.

In conclusion, aducanumab offers real
clinical benefits to millions of AD patients who currently are devoid of a meaningful therapy. Additional delay is unwarranted. We strongly encourage the committee to recommend its approval. Thank you.

DR. FOUNTAIN: Thank you.

Speaker number 14, your audio is now connected. Will you introduce yourself? Please state your name and any organization you represent for the record.

MS. MONTANA: Thank you. My name is Pam Montana, and I have no conflicts of interest, and I'm speaking on behalf of myself and my family, and I want to thank you for this opportunity today.

I have early stage, early onset Alzheimer's. I was diagnosed in 2016 after many, many months of cognitive testing, brain scans, and MRIs. My symptoms actually started in 2014, but unfortunately my doctors dismissed my symptoms because I was so young. It wasn't until my husband accompanied me to an appointment with my neurologist and shared stories of me repeating
myself and not remembering conversations that we 
finally got some help. I live in the Bay area, and 
thankfully UC San Francisco's research department 
was able to confirm my diagnosis. I don't have a 
family history of dementia, so when I started to 
experience changes in my memory and thinking, 
Alzheimer's wasn't on my radar. 

I was at the peak of my career, loving life, 
managing and leading teams, and creating programs 
to help women advance at Intel Corporation. I 
started to struggle and to learn new information 
and to remember conversations. I began to rely 
heavily on notes versus memory, something I never 
needed to do before. While my family and friends 
dismissed my symptoms, I knew something was wrong, 
seriously wrong, and it was terrifying. 

I wish I could say that this diagnosis 
brought relief to my family, but there was none. 
We are one of those close, boisterous families and 
together we cried and cried. They shared their 
disbelief and their overwhelming grief at the 
thought of my eventual decline. I hate to think of
the pain and sadness this disease will inflict on them as I start to deteriorate and need more help.

I felt like the rug had been pulled out from under me. Everything was fine today, and then the next it wasn't. That night instead of thinking about dreams for my future, I was making plans for my funeral. My family has made a conscious choice to focus on the present, but that doesn't obscure the reality of this devastating disease. My diagnosis of Alzheimer's has shattered my world, taken away my freedom and my ability to work, and it will eventually rob me of my ability to think or to remember.

There are many, many stories like mine across this country, many men and women hoping and praying for a cure or to be selected for a clinical trial that could potentially slow down the progression of the disease. It's time for those of us living with Alzheimer's to hear some good news. We need hope that there will one day be a cure. We need hope that there will be a drug treatment that can slow down progression. We need
hope that the 5.8 million people living with Alzheimer's have faith that drug trials can and will make a difference for them and their family. Thank you for this opportunity to speak with you.

DR. FOUNTAIN: Thank you.

Speaker number 15, your audio is now connected. Will you introduce yourself and state your name and any organization you're representing for the record?

JUDGE BROOKS: Hello. I'm retired Judge Nelson Keith Brooks of the California Superior Court system and a victim of Alzheimer's disease. I've been asked to speak here today on two issues regarding my experience with this disease. The first is how Alzheimer's has affected my life, and the second is why a drug like aducanumab is needed in the fight against Alzheimer's. Simply put, Alzheimer's has turned life upside down for me.

At the time of my diagnosis, I was a sitting superior court judge here in California. My job in a nutshell was to make decisions for the parties appearing before me as to how to resolve disputes
that had arisen between them which they could not resolve on their own. As a result of my diagnosis of Alzheimer's, I was compelled to resign my position and retire early rather than risk challenges to my decisions based on any assertion of lack of mental competence arising from my condition.

When I received my Alzheimer's diagnosis, I was disheartened to learn that no protocols nor medications were available to reverse or even slow down the inevitable decline in brain function. The high toll this disease takes on its victims and their families, both physically and financially, evokes thoughts of the inevitable demise of my independence and mental capacity and the resulting increased burden on my family.

I am one of the lucky few who has been accepted into the trial for another immunotherapy anti-tau drug at the University of California San Francisco. This trial has given me further hope to slow the progression of my disease as well as the possibility of potential treatment for those yet
undiagnosed.

The urgent need for the approval of drugs such as aducanumab to fight Alzheimer's disease should be more than apparent. I cannot emphasize too strongly the importance of the swift approval of aducanumab, and I should state that I have no financial relationship with the sponsor, Biogen.

DR. FOUNTAIN: Is that the end of your comments?

JUDGE BROOKS: Yes, it is.

DR. FOUNTAIN: Okay. Thank you. Thank you very much.

Next is speaker number 16. Speaker number 16, will you introduce yourself? State your name and any organization you're representing for the record.

MS. WHITING: Hi. Good afternoon. My name is Grace Whiting, and I am the president and CEO at the National Alliance for Caregiving. We're a 501(c)(3) nonprofit organization and coalition in the DC area, and our mission is really to build partnerships in research, advocacy, and innovation.
that can make life better for family caregivers.

In terms of disclosures, we are not taking any position on the approval of this drug but we wanted the chance to offer context for considering the use of data that might be provided by a family caregiver, someone who's an informal friend or family member and supporting a person with dementia with activities of daily living.

I also would like to disclose that Biogen is a current member of the National Alliance for Caregiving. In FY2019, they contributed membership dues as did several other corporations and not-for-profit organizations. Those dues were roughly 2 percent of our total revenue, and we anticipate that they will renew their membership this year and that income will be approximately 1.6 percent of our total revenue.

I'll also mention that there's more detail in a written comment that we submitted, but I'd like to highlight a couple of key things when you're thinking about this issue. The first is I just want to say thank you. Thank you for thinking
about caregivers. Thank you for the work that the FDA has done in June of this year talking about the caregiver's role in medical product development.

Based on our understanding of the regulatory framework, we think there are three cases when caregivers can report data: when the person can't report for themselves; to ensure that the person's wants, needs, and preferences are honored; and to provide observable information about a patient's experience. With that context, we would urge the FDA to look at, in this study, the 7 of 9 clinical outcome assessment tools that have caregiver input and ask three questions.

First, is there evidence that caregivers can be reliable reporters of equivocal data for the specific measurement tools that are included in this study? Second, to what degree does the caregiver's voice complement rather than supplant and replace the voice of the person living with dementia? And third, what is the relationship between reducing caregiver strain and the medicine's impact on the overall burden of disease.
on the family?

In particular to that last point, we know that dementia caregivers have higher levels of stress, depression, and anxiety than others, and that the more stress they're under, the more potential there is potentially for the person with dementia to be institutionalized or even subject to abuse. So any pharmacological intervention needs to be considered with an understanding of the holistic need of the family, of the person with dementia, and of other ways to treat the disease. Thank you so much for your time.

Questions to the Committee and Discussion

DR. FOUNTAIN: Thank you.

The open public hearing portion is meeting has now concluded. We will no longer take comments from the audience. The committee will now its attention to address the task at hand, the careful consideration of the data before the committee, as well as the public comments. I want to take a moment to just personally express my gratitude for all those who came forward for the public comments.
I recognize sometimes those are difficult things to say in public and to recognize, and it's very much appreciated by the committee.

We'll now turn our attention to the questions at hand. I'd 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. I'll open the question to discussion.

Discussion point number 1, the primary evidence of effectiveness presented in support of aducanumab for the treatment of Alzheimer's disease is provided by Study 302. Discuss the evidence of effectiveness provided by Study 302, viewed independently and without regard for Study 301, with particular consideration of the size of the study, design of the study, analysis of the results to assess the effects of the drugs, and consistency of results among various subgroups in the study.

So before we discuss the specific content, the question, before we discuss all this, is there any issue that needs to be raised or clarified.
about the wording of this discussion point?

I see that Drs. Alexander, Emerson, and Kryscio have their hands raised. I'm not sure if that's from before or from now. So if you have your hand raised and you're not asking about now, if you'd please put your hand down.

Alright. Dr. Alexander?

DR. ALEXANDER: Thank you. Can you hear me?

DR. FOUNTAIN: Yes.

DR. ALEXANDER? Okay. I wanted to ask a question of the FDA earlier, and it's relevant to this question. I guess the bottom line is that I find the materials that the FDA has provided strikingly incongruent, and I have a very hard time understanding, after carefully reviewing, what I thought was a very well done and well articulated biostatistical review, which convincingly argued the evidence was, quote/unquote, "At best, compelling include that there are substantial evidence of effectiveness," and in particular that Study 302 provides, quote/unquote, "a robust and exceptionally persuasive study."
It just feels to me like the audio and the video on the TV are out of sync, and there are literally a dozen red threads that suggests concerns about the consistency of evidence, a dozen. For every point that you can find suggesting support, there's another point or two that raises concerns. So there's only one time point with statistically significant different findings from placebo. Forty percent of the ITT analysis didn't have the opportunity --

DR. FOUNTAIN: Let me interrupt you for just a moment. So the first question hand is do you think we need to change any wording in this discussion before we talk about --

DR. ALEXANDER: Well, the FDA wants to take a totality of evidence approach and seems to toggle back and forth between saying this is just about Study 302, and then selectively identifying elements of Studies 103 and 301 to support an assertion that 302 is robust, and I don't think that you can look at 3:02 in isolation.

There have been some very good questions
about this already that highlight the inconsistency of findings across these three studies. So I understand the question, but I'm not convinced that this is where we should be focusing our time.

DR. FOUNTAIN: Well, I think that's under the discussion point. If we don't think there's anything to change the wording of the question, we can just turn to the discussion. So let's say that that doesn't alter the wording at the moment and that's part of the discussion.

So let me just ask if Dr. Emerson has a question about the actual wording of the question or about the response to the question.

DR. EMERSON: I do have a question about the wording.

DR. FOUNTAIN: Sure.

DR. EMERSON: They ask us to talk about 302 by itself, which I can do, but it has to take into account that this is the most exciting of results of two studies, and I need to make certain that the FDA is aware of that as they ask this question. And then part of this, I guess we could ask
Dr. Dunn to tell us what he thinks the p-value is from the primary analysis in 302, and this will tell me a lot about whether he's thinking that 302 independent of 301 means pretend that 301 was never done or whether it means adjust the inference to allow for the fact that this is the best of two studies.

So Dr. Dunn, if you wouldn't mind telling me what you think the p-value is for the primary endpoint, that would help a lot.

DR. FOUNTAIN: And how would you change the wording of the question based on that? Because the wording of the question says "viewed independently," so you might assume the question is assume 301 was never done. That's how I would read that.

DR. EMERSON: I would not. I would not. I can do valid inference on what we call extreme value statistics, the idea of give us what the sampling distribution is when it's based on this, yet only use the 302 data.

DR. FOUNTAIN: So that's the nature of the
question, and I think maybe we could save that for
the discussion about whether or not that's --

DR. EMERSON: No. This is important. This
is a very important question because if we are to
pretend that 301 never existed, well, we can talk
about the scientific rigor and departures from
that, that such would be. But for instance, you
could say that we adjusted for that statistic by
saying that the p-value is not 0.012 but it's
closer to 0.024, still ignoring some multiple
comparison issues but at least adjusting for the
major aspect, in which case I can answer this
question based on that. But I would hate for a --

DR. FOUNTAIN: Okay. So you --

DR. EMERSON: -- [indiscernible].

(Crosstalk.)

DR. FOUNTAIN: Right. So you'd advocate to
review that you'd like to remove the term "viewed
independently and without regard for Study 301" or
to know that it should remain intact because you'll
answer differently.

DR. EMERSON: Well again, we can talk about
the sampling of 302, what the true sampling
distribution was for 302, or we could talk about
302 with 301, taking both results. One result is
saying 302 is the best of two possible studies.
That's one sampling distribution. Another is
saying we're going to look at 302, just the 302,
and recognize that 301 carries the exact same
weight and eventually would be taken care of in a
meta-analysis.

My interpretation is the FDA wants us to
imagine that we can look at 302, just those
results, but we need to recognize that that is the
best of two studies conducted concurrently. And
again, if Dr. Dunn will tell me what his persuasive
evidence means -- I heard "persuasive evidence" far
more often than I heard what any results were, just
conclusion. But if he'll tell me what his
persuasive evidence is in terms of the p-value that
he was looking at on that primary endpoint -- I
realize there's totality of evidence, but I just
want to know was he taking into account that that
was a p-value that was approximately 0.024 or was
he taking into account the erroneous conclusion
that that was a p-value of 0.024.

DR. FOUNTAIN: Okay. So is that question
subsumed under Dr. Duda? Dr. Duda also had his
hand raised. Does that subsume your issue as well
or do you have an independent issue on the wording
of the question?

DR. DUDA: I have an independent question.

DR. FOUNTAIN: Maybe you can ask that and
then we'll see if we can put them together.

DR. DUDA: Sure. With regard to the
statement for the treatment of Alzheimer's disease,
I'd just like some clarification if they're asking
us if this is a disease-modifying treatment, or a
symptomatic treatment, or both, which way that they
would like us to consider that statement.

DR. FOUNTAIN: Okay. So you'd like a
qualifier before treatment of Alzheimer's disease,
the treatment of the symptoms of Alzheimer's
disease, or treatment of the pathophysiology of
Alzheimer's disease, or treatment of the
progression of Alzheimer's disease? Is that the
kind of thing you're asking about?

DR. DUDA: Yes, that would be helpful.

DR. FOUNTAIN: Okay. I imagine the answer is going to be -- I guess we can word that anyway we want it, in a way, and then propose that. So maybe we could turn our attention to Dr. Dunn and ask for comments on those two things.

Would you like a qualifier before Alzheimer's disease and do you want us to really view it independently without regard for Study 301?

DR. GOLD: I'm sorry. Before we wordsmith the question, can we go through the rest of the folks that have issues with the wording?

DR. FOUNTAIN: Yes. I'm sorry. I didn't see the hand raised. Dr. Gold?

DR. GOLD: Yes. I have a particular issue with the viewed independently and without regard for 301 since those studies are identical in design, identical in inclusion/exclusion criteria, and identical presumably in biomarker analysis. So I have real serious issues with how you can divorce the two studies from each other.
DR. FOUNTAIN: Okay. The question, you would like to us -- I'm having trouble what it is we're going to ask --

DR. GOLD: You can do it independently --

(Crosstalk.)

DR. FOUNTAIN: Do you want us to remove the phrase "view independently without regard for Study 301," but I think that's the nature of the question. I'm having trouble how to --

DR. GOLD: Correct.

DR. FOUNTAIN: -- understand that.

DR. GOLD: Thank you.

DR. FOUNTAIN: Dr. Kryscio?

DR. KRYSCIO: I'm going to reserve my questions for a little bit later on when we get to 103.

DR. FOUNTAIN: Okay. And about the clarity of the question from Dr. Onyike?

DR. ONYIKE: Thank you. Yes. I think I echo what Dr. Gold just asked. And beyond that, I read this question as speaking specifically to data and not at all speaking to the testimonies we just
had. I just want clarification.

DR. FOUNTAIN: I think that's correct. Yes.

The question's to discuss the evidence, so that
means the evidence we know about, of the
effectiveness, as we know effectiveness, to be
provided by Study 302 -- that's the study called
302 -- viewed independently without regard for
Study 301 -- that's the other study -- with
particular consideration of the size of the study
and these other issues. The question is, is the
question clear and can we do that?

So I guess the issue has been raised about
is it possible to view independently without regard
to Study 301? Is that the nature of the question?
I think that the original issue was to make clear
that you might not want to do that, but I think
this is a question for the FDA and then a
discussion and question, and voting I think is
where we can declare what we think. In other
words, if we have a specific point of clarity we
need from Dr. Dunn, we can ask him, but I'm not
quite sure what it is we're asking.
Does someone have a specific point of clarity?

DR. EMERSON: If I can clarify again, it's possible that if you tell me you are analyzing the best of two studies, I cannot know anything about the other study except for the fact that it wasn't the best, and I can talk about what the results are. And in that case, the p-value of the primary endpoint is something 0.024 or higher.

On the other hand, you could say pretend that Study 301 never existed. Imagine a world in which 302 was there. Now, I think that's a silly question to ask given the history, but the idea of just wanting to stress that we can view independently the results of 302, recognizing that it's the best of two studies without ever knowing what the results of 301 was, without knowing --

(Crosstalk.)

DR. FOUNTAIN: I think that's pretty clearly the nature of the question. I think the nature of the question is pretend like 301 -- in your wording, pretend like 301 didn't exist and just ask
about 302, because in the subsequent questions we're getting clarity on that, and then a consideration is how does that change your mind.

DR. EMERSON: But again, I don't think it is the same. I'm going to choose two numbers and only tell you what the highest number I chose was. That has a different sampling distribution than if I just choose one number and tell you what it is. So again, I just want it clear, because I have a problem with this entire question unless it's recognized that the p-value that was being reported throughout this thing of 0.012 is not a true p-value. But if you wanted us to do this, it would be possible in a prespecified matter to tell the FDA I'm going to do two studies and I'm only going to give you the results of the best one. We can compute p-values, we compute confidence intervals, and we can do all sorts of things there. Not many of us really do that.

DR. FOUNTAIN: So I think your position is clear. I think we have to answer the question we're asked, and then we can discuss in our voting
how we voted and how that influenced our vote.
Because if we just eliminate the question, I don't
think that will be helpful. I think the reason for
the questions and discussion are to get at those
kinds of points to make clear what we think. So I
think we just have to clearly understand what
they're asking whether you agree or like it or not
because then we have the opportunity in the voting
to decide what we think of that.

DR. EMERSON: Well, I would then like to
just register that I have not been super impressed
with how the briefing book and presentations have
gone from the FDA for this study. I feel that, to
a certain extent, the clock has been run out and we
haven't been able to ask questions because mainly
the FDA just gave us conclusions and not results.

So now we have trouble discussing this
because it's all being supplanted by saying look
over here and answer this irrelevant question, and
we aren't really going to give you the opportunity
to say how this study should be interpreted if we
want to ignore the numbers from 301, but we may
never, ever, ever, ever ignore the fact that 301 
was done.

DR. ALEXANDER: This is Caleb Alexander, and I agree with that assessment, and I very much would like to get into some details here about the totality of evidence and about the conclusions that the FDA seems to be reaching, and about, as I said, the incongruous materials that have been provided, and dozens of questions that we really haven't had a chance to ask the FDA about.

In particular, I'd like to query the FDA about any number of concerns that their own statistical reviewer have identified, and that I have not yet heard either an adequate response from the sponsor, but more importantly from the FDA regarding their own interpretation of those reviews.

DR. FOUNTAIN: Okay. We can discuss that here and then vote because I don't think we're going to be able to get to the voting unless we do. So I think we should have some open discussion on this question, among others, and I think we've
heard clearly so far that there is an idea that 302 can't be viewed without thinking 301.

So now let's move to Dr. Thambisetty, if you still have a question.

(No response.)

DR. FOUNTAIN: Comment?

Your phone is on mute if you're asking a question, Dr. Thambisetty. You have to unmute it in the upper-left corner.

DR. THAMBISETTY: Thank you, Dr. Fountain. Can you hear me now? I'm sorry about that.

DR. FOUNTAIN: Yes.

DR. THAMBISETTY: So I completely understand the points that Dr. Emerson and Dr. Alexander have made, and in fact I shared a similar concern. But I take some measure of comfort from discussion number 7 and its accompanying both because I think that sort of gets to the point that we are trying to resolve here, because in the text for discussion 7, we are clearly allowed to discuss the impact of the results of Study 301 on the consideration of the results of Study 302.
(Automated interruption.)

DR. SMIRNAKIS: This is Karen Smirnakis with Biogen. I'm back on.

DR. FOUNTAIN: I think everyone was disconnected, so we're going to get back on to resume your comments.

DR. BONNER: Yes. This is LaToya Bonner, DFO. Do you hear me?

DR. FOUNTAIN: Yes, we hear you.

DR. SMIRNAKIS: Okay. I can just make sure all of our --

DR. BONNER: Yes, if you can, please.

DR. SMIRNAKIS: Yes, we're all back on here.

DR. FOUNTAIN: It looks like all of the committee members are back on as well.

Dr. Thambisetty was about to speak. You ended up giving your comments I think.

DR. THAMBISETTY: Great. May I continue, Dr. Fountain?

DR. FOUNTAIN: Yes.

DR. THAMBISETTY: I share the satisfaction and the concern about the wording of this question,
but I take some measure of comfort from the text for discussion point number 7, which to me looks that it gives us ample opportunity to discuss the impact of Study 301 on the results of Study 302. I know that. So as I have said, I hope I'm not speaking out of turn, but I think there is going to be ample opportunity for us to discuss 301 and 302 together.

DR. FOUNTAIN: Yes, that's right. So I guess maybe that's another way to view it. I understood, so I'll take the prerogative to speak now. And I think there's no one else with their hand up. But if you're done, Dr. Thambisetty, you could put your hand down if you would.

DR. THAMBISETTY: Yes.

DR. FOUNTAIN: I think the nature of this question is it would say -- I read this question to be, if you look at Study 302, is it a positive study? And in my view, yes, it's a positive study because it's designed well, analysis looks appropriate, consistency in the results, et cetera, if you view it in isolation. If there was a single
study as was intended prospectively designed, that makes it positive, unless you have concerns about stopping early and so forth, or something about the way it's analyzed.

So I think the nature of this question is just look at 302; is it a positive study? That isn't what it says exactly but I think it's discussed, how I interpreted that, because then it gets down to the other issues as Dr. Thambisetty was saying. So maybe we could look at that as a way to consider this question so we can get on to the other issues that you've brought up that are very relevant.

I think Dr. Alexander is next.

(No response.)

DR. FOUNTAIN: Dr. Alexander, can you turn your --

DR. ALEXANDER: I'm sorry. Thank you. Can you hear me now?

DR. FOUNTAIN: Yes.

DR. ALEXANDER: Thank you.

So I will speak only to 302 and resist the
inclination to do otherwise. I think even with Study 302 there are some reasons for question. One is that there's no correlation between plaque reduction and week 78 outcomes. I think this is a good example where it feels a little bit like people want to have it both ways. In other words, there's an argument that molecular mechanisms provide a strong support of body of evidence to back up 302 as a robust, exceptionally persuasive study, but there's also a disclaimer that no formal claim of biomarker is being made, and no ability to explain why there's no correlation between plaque reduction and outcomes.

A second source of concern about 302 is that the major stratum driving the findings, up to a third of patients had a mid-study dose increase and more unblinding or potential unblinding. A third is that the placebo response before and after Amendment 4 are completely separate among at least some subgroups, suggesting that these dose increases are entangled with placebo worsening.

A fifth is that, as was pointed out by the
FDA's own reviewer, the failure of the low-dose arm in 302 means that technically the secondary endpoints for the high-dose arm are not interpretable, and even if they are, they're moderately correlated. Then the last that I'd say is that, once again as pointed out by the FDA's own reviewer, there's no consistent effect across subgroups in 302, yet one would hope to see this with a strong efficacy signal. So these are five concerns about Study 302, even ignoring the fact that other studies have been performed.

DR. FOUNTAIN: Okay. I think those all makes sense that are pointed out by the reviewer. From my perspective, there's a rough correlation with several things. We saw amyloid plaque does decrease with treatment and it does separate in the groups. So in the big picture there's just a lot of negative [indiscernible] information.

(Crosstalk.)

DR. FOUNTAIN: I'm sorry. Next is Dr. Gold.

DR. GOLD: Yes. I'm assuming we're already in the discussion. I think part of my concerns
about 302, if I talk about it in isolation, is what happened pre- and post-amendment and the actual numbers of subjects. And again, I'm sorry; 301 comes into it because it's a question of who was being enrolled and what happened.

I will stipulate to these studies were well designed, and I think there's no question with the design of the study. Part of the question I have is on the execution of the study. Some of the material that Biogen actually presented at the CTAD meeting a year ago, where they actually showed that when they made the amendments, these amendments did not get implemented overnight, it took a long time, and in fact there was a lot of heterogeneity in how the amendments got implemented.

I just would like to get more clarity on exactly how the amendment really impacted 302 because if you think about it, the amendment only impacted ApoE4 subjects at the highest dose, but there's evidence from looking at the ITT analysis and for the post-Amendment 4 population that was in effect on the low dose in the 302 study, which
makes absolutely no sense to me. And again, it's material that that Biogen presented at CTAD.

So if you start to see changes in the low dose on the primary outcome measure from the ITT population versus the post-Amendment 4, you have to wonder whether everything in the high dose is noise. So I really would like to understand a little bit more. And again, if we're going to look at 302 in isolation, how the actual amendment affected it.

The other part, if I may, we kind of danced around it. The study was declared futile. Subjects were brought to close-out visit. There's a huge amount of missing information which, again, has been referred to by both the sponsor, the FDA, and the statistical reviewer, but I've heard no discussion about whether the pattern of missingness actually has any bearing here.

So it would be helpful to understand whether the analyses and the effect -- really, do we actually believe that these data are missing at random? Because that seems to be the assumption
that was made in the analyses, where the FDA reviewer was clearly saying, hey, there are red flags here that these data are missing not at random. So I'd like to get some clarity on some of those questions since we're already into the discussion of the study itself.

DR. FOUNTAIN: Those are questions you've raised about whether or not the missing data is non-random.

DR. ALEXANDER: Correct.

DR. FOUNTAIN: The sponsor did provide I think three different analyses looking at the non-random data that didn't --

DR. ALEXANDER: No. I'm sorry. They provided the random sensitivity analyses, but there's no diagnostic for missing not at random. And I really would like to hear from the FDA statistical reviewer on whether studies that are terminated for futility can really be expected to have missing data at random, which is how these data were analyzed.

DR. FOUNTAIN: Okay.
Next, Dr. Duda?

DR. DUDA: I guess I'm going back to what I was saying before. The way you couched the question, Dr. Fountain, was it a positive study? But that's not what we're being asked, and I think we need to make that distinction. We're being asked if it supports the effectiveness of aducanumab for the treatment of Alzheimer's disease. Whether or not it met its primary outcome criteria is not the same as answering that question, I think, for some of the reasons that have already been raised by others, and I'll stop there.

DR. FOUNTAIN: I'd agree with that, too. As for evidence of effectiveness, I'm just saying it's a positive study at face value and take that as evidence of effectiveness.

Next is Dr. Kesselheim.

DR. KESSELHEIM: Hi. Some of the points that I was going to raise have been raised by others, but I just wanted to also make the point that analysis of this question is challenging for
me because we wouldn't be analyzing Study 302 in isolation unless 301 existed because 302 is half, or even at best two-thirds of a study. It was stopped for futility. And if it would have existed by itself, it would have never been stopped for futility. It would have been continued until the final results were in. So it's strange to rely on half or two-thirds of a study as your evidence of effectiveness for a drug.

DR. FOUNTAIN: You mean about 302 or 301?


DR. FOUNTAIN: What do you think about just this value of a positive statistical result with a smaller angst [indiscernible] has a bigger effectiveness than anticipated?

DR. KESSELHEIM: I think that's another issue to discuss just in terms of the way that the results are framed. Much of these results are framed in the context of percentage changes from placebo. The actual real effect size is on the order of change in 0.4 on an 18-point CDR-SB scale. So I think that's also a relevant issue to think
about.

DR. FOUNTAIN: Okay. Actually, I think we're back to Dr. Emerson, who I went around the horn before getting back to.

DR. EMERSON: So I'm going after this question, again, just to say imagine that their primary endpoint had been saying we're going to take the best of two studies, in which case it all comes down to do we accept the p-value of 0.024 instead of what might be usual for a pivotal study of 0.01 or less? There's not any set rule. The things that would go into this are how all the data hangs together, what the unmet need is, and so on.

Just to make clear, I do have a medical degree, but I am a biostatistician. But more importantly in this, I have family members who had very severe Alzheimer's, and I've watched my mother-in-law degenerate from a very vibrant person to somebody who is just a complete invalid over a space of 18 years. So I understand what there is, and that does influence whether I would take the 0.023 -- or 0.24, and this is best probably a
minimum p-value that's there.

I'm not going to get into the other things, other multiple comparisons. But what is the internal consistency? What are the other things that make me believe that we might count this as a pivotal study? Some of the things are the dose-response relationship. That's one of Koch's postulates and it's in the right direction. Of course, there's only so many things that three dose groups can present that's not there.

I will also concede the hypothesis that's very intriguing, that the oligomers are a more important target, but that's something that also has to be proven. So I can't immediately discount the relevance of the former failures based on monoclonal antibodies to monomers, but it's very intriguing, something to be proven. It's something that showed forethought prespecification, so that's why I attach a little bit of weight there.

The internal consistency of the secondary endpoints, we saw for about two seconds a slide about the principal components analysis that I was
just trying to figure out, and they quickly say "slide down" and it goes away. But some of the points that they were trying to make are partially valid, which says if you look at all of the different components of the four major measures, the different components don't necessarily have overlap.

However, as shown in the FDA statistical approach, there is high degree of correlation. If I could have asked more questions, I would have asked how that correlation might have differed across treatment groups because that can also be an indication of how the treatment is acting on things and whether there's common pathways. But at the end of the day, principal components analysis was not what was being analyzed as we look at the secondary endpoint, so the overall correlation is the only thing we have.

I would have loved to see also a mediator analysis on whether the changes in plaque explain much of the differences in the cognitive endpoints, which is of course the burden of proof. The burden
of proof is we targeted the oligomers of the amyloid hoping that that would have an impact clinically, and our question is does that bear up; if it's a strong enough effect? I must say I care more about the clinical aspects than I do about the --

DR. FOUNTAIN: Right.

DR. EMERSON: -- pathology.

But these are the things that sort of have me down saying it's not quite enough to say that this is a pivotal study.

DR. FOUNTAIN: I think that's an excellent summary of our discussion on this particular first question, and that is, to be crude about it, none of us like it, but if you force it to disregard 301, it appears that 302 could be positive and that there is evidence of effectiveness. But this subcomponent analyses, while they seem to support it aren't necessarily overwhelming, is what I think I understand the general discussion to be, with thoughts among all the different details and subcategories we talked about.
I'd just take my prerogative of one final comment that there is a dose response, it appears, in 302 for amyloid reduction based on the information we were given. So I'm just agreeing with your last point that there are some trends towards that.

We do have limited time available, and we do want to address the questions we're asked, so let's turn to the vote in the time that we have.

DR. PERLMUTTER: You know, I haven't been called on, and my hand's been up.

DR. FOUNTAIN: Oh, I'm sorry. Who is that?

DR. PERLMUTTER: Joel Perlmutter.

DR. FOUNTAIN: Okay. Dr. Perlmutter?

DR. PERLMUTTER: I just want to make a couple of points. First of all, I do think that having this discussion point is being foist upon us and is artificial. The specific points about 302, I'm concerned about describing the benefits as multiple endpoints when I do believe we saw data that they are correlated; multiple endpoints are correlated. I think we see a lack of correlation
between the A-beta change and the clinical endpoint CDR-SB. I think that's a concern.

I think the retrospective application of the definition of rapid progressors makes a concern for me and the differential unbinding in people getting the high dose. I think these all raise questions. Even if we don't see statistical difference on the unbinding, when you add these things up, they can together cumulatively be an issue, and we saw that with just small groups of rapidly progressors removed in other places.

So this analysis is very sensitive to small changes in the numbers in which people are being included and excluded, so I'm very concerned about this.

DR. FOUNTAIN: Okay. I think it's important that we don't think anything is foist upon us. The purpose of this discussion is to have the discussion we're having that raised the concerns in the relevant areas and not -- and you can disagree or agree. And now we're about to vote on a very specific --
DR. THAMBISETTY: Dr. Fountain, may
I -- Dr. Fountain, I have not had a chance to weigh
in on this question either, so I'm just
wondering --

DR. FOUNTAIN: Let's make this our last
comment.

Dr. Thambisetty?

DR. THAMBISETTY: Yes.

DR. FOUNTAIN: Okay. So you can have a
brief comment and then we'll move on to the vote,
because in the vote we get to discuss more about
our own opinion about it.

DR. THAMBISETTY: Okay. I have significant
cconcerns about characterizing Study 302 as being
either robustly positive as described in the
briefing materials or as characterizing it as a
home run, which is what I thought I heard earlier
in the morning. So if I'm given an opportunity to
elaborate on why I'm concerned during the course of
this meeting, I'd like to do that.

Are you suggesting that I expand upon why
I'm concerned right now or after we vote?
DR. FOUNTAIN: If you have additional concerns we haven't discussed, then you can say them right now.

DR. THAMBISSETTY: Thanks. My main concerns are with regards to the potential effect of unblinding of patients and caregivers. I think that's a huge concern with the study. Thirty-five percent of patients exposed to the drug developed ARIA, so it's inconceivable that patients and caregivers who are given a diagnosis of ARIA and who are then subjected to very intense serial MRI surveillance, which happens every month until the abnormalities are resolved, are going to be unblinded to the treatment.

What makes this especially concerning is that the primary endpoint, which is the CDR sum of box scores, is entirely dependent upon subjective information that is provided to the rater by patients and their caregivers, and the same goes for the secondary endpoints like the NPI or the ADCS-MCI scale. These scales are very, very sensitive to biases due to expectations on the part
of patients and caregivers when they realize that they're on the treatment arm which is very likely to have occurred when you're being called in to come in for additional MRI scans because you have a drug-related adverse event.

I really think the fact that these potentially unbiased patients and caregivers are then providing subjective information about behavior and function that determine their scores on the primary endpoint, as well as key secondary endpoints. There's a big concern that I don't think has been adequately addressed.

The fact that the raters were blinded is really immaterial to this particular question because the information that the rater uses comes entirely from patients and caregivers for some of these scales. I think that is one concern.

DR. FOUNTAIN: So that's a concern about unblinding.

DR. THAMBISETTY: Correct.

DR. FOUNTAIN: Do you have any other specific concerns you might talk about before the
vote?

DR. THAMBISETTY: I have one additional point about minimal clinically important difference which I think is relevant in terms of the magnitude of the effects that are being reported. I think the concept of minimally clinically important difference is very relevant to dementia clinical trials. The fact that several of these outcomes are reported as relative differences in terms of percentage points in comparison to placebo make this slightly difficult to interpret because the strongest result is a relative difference of negative 0.39 points from placebo in the CDR sum of box scores.

This is also present as a relative difference of 22 percent from placebo. But what do these changes mean in terms of their functional significance? Do they represent tangible real-world benefit? Are they clinically important? This is what is captured by the concept of minimal clinically important difference, and that's defined as a smallest difference in score and the domain of
interest, which patients perceive as beneficial and which would mandate in absence of any troublesome side effects and cause a change in patient's management.

There is empirically derived evidence for what constitutes minimal clinically important differences in dementia clinical trials. There's one paper that was just published by Andrews et al. in Alzheimer's and Dementia, which suggests that the MCID for patients with MCI, there's a change in CDR sum of box scores or MMSE of one point and for patients with mild Alzheimer's disease of two points. And if you use that as a yardstick, these changes are extremely small.

DR. FOUNTAIN: Yes. So you think that it's not necessary clinically meaningful because it's such a small --

DR. THAMBISETTY: That is correct.

DR. FOUNTAIN: I think we have the opportunity now to ask the FDA a question about the correlation of amyloid with clinical change in Study 302. I'm not sure who's -- Dr. Dunn,
Dr. Krudys, or someone else is going to address that.

DR. KRUDYS: Kevin Krudys here about the correlation. So there is a correlation if you include the placebo and the low-dose data. I think what you saw in the stats documents was the correlation for just at the high dose. So you do see a correlation if you include the entirety of the data, and you did see a correlation in Study 103 across the doses there. So I just want to point that out.

Second, I think in terms of correlation, you have to realize that the changes in the biomarkers are changing over time and it's just a snapshot of what we see at week 78. There could be a delay between the change in the biomarker and the change in the scale like CDR-SB, so that's not taken into account. I know the sponsor has done some work with the model that can describe the time course in terms of the change in the reduction of brain amyloid versus CDR-SB, and they did find a relationship.
So those are few things I think the committee should keep in mind in terms of thinking about the correlation. And second, I'll just say that it's not like change in beta-amyloid are being used as a surrogate here. It's a biomarker of what the drug is doing, and there is some correlation between the changes and changes of clinical outcomes.

DR. FOUNTAIN: Okay. Thank you.

So now we can move to the vote, and remember at the vote we also have an opportunity to explain our vote as well. So it's not as though we're not going to discuss these things anymore, but the questions provide sort of a roadmap, as I think Dr. Thambisetty was saying, to narrow down some of these points.

We can move on to the next question, which is a voting question, and Dr. LaToya Bonner will provide the instructions for the voting.

DR. BONNER: For the record, LaToya Bonner, questions 2, 4, 6, and 8 are voting questions.

Voting members will use the Adobe Connect platform
to submit their vote for this meeting. After the
chairperson has read the voting question into the
record and all questions and discussions regarding
the wording of the vote question are complete, the
chairperson will announce that voting will begin.

If you are a voting member, you will be
moved to a breakout room. A new display will
appear where you can submit your vote. There will
be no discussion in the breakout room. You should
select the radio button. That is the round
circular button in the window that corresponds with
your vote, yes, no, or uncertain. You should not
leave the "no vote" choice selected.

Please note that you do not need to submit
or send your vote. Again, you need only to select
the radio button that corresponds to your vote.
You will have the opportunity to change your vote
until the vote is announced as closed. Once all
voting members have selected their vote, I will
announce that the vote is closed.

Next, the vote results will display on the
screen. I will read the vote results from the
screen into the record. Thereafter, the chairperson will go down the roster and each voting member will state their name and their vote into the record. You can also state the reason why you voted as you did if you choose. However, you should also address any subparts of the voting question if any.

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

(No response.)

DR. BONNER: Okay. I will now turn the meeting over to the chair.

DR. FOUNTAIN: Okay. Question number 2, does Study 302, viewed independently and without regard for Study 301, provide strong evidence that supports the effectiveness of aducanumab for the treatment of Alzheimer's disease?

Any clarification needed for the nature of this question?

(No response.)

DR. FOUNTAIN: Okay. So if there are no further concerns about the wording of the question,
we'll now begin the voting on question 2.

DR. BONNER: We will now move voting members to the voting breakout room to vote.

(Voting.)

DR. BONNER: Voting has closed and is now complete. Once the vote results display, I will read the vote results into the record.

The vote results are displayed. I will read the vote with totals into the record. For question 2, 1 yes, 8 nos, 2 abstentions.

DR. FOUNTAIN: Thank you. We will now go down the list and have everyone who voted state their name and vote into the record. You may also provide justification of your vote if you wish.

We'll start with Dr. Kesselheim.

DR. KESSELHEIM: This is Aaron Kesselheim. I voted no. I think a lot of the reasons I voted no were discussed in the discussion period, so I'm not going to be able to go through all of them in detail. But I think the fact that this was not a full study, there is a suggestion of an effect but there are enough red flags in terms of the changes
to the protocol, the concerns about unblinding, and
the observation of the effect in the 78-week
analysis. Without a full cohort of patients being
able to contribute to that analysis, to me doesn't
add up to a strong evidence.

DR. FOUNTAIN: Next is me, Nathan Fountain.
I voted yes because I think in isolation, without
regard to 301, 302 was a positive study. It met
its primary endpoint, even on a smaller end than
anticipated. I think there are lots of small
issues with it, but the trends I think are all in
the right direction. So I think on its face value
alone, 302 I think is positive and provides
evidence, and I think relatively strong evidence by
itself.

Next is Dr. Duda.

DR. DUDA: I voted uncertain, which I guess
I would argue whether or not that would mean I'm
abstaining. I'm abstaining from committing either
way I guess. But I agree, I think it was a
positive study. It met its primary outcome even
though it was truncated early. I, however, still
have concerns that prohibit me from saying that there's strong evidence.

DR. FOUNTAIN: Dr. Perlmutter?

DR. PERLMUTTER: Yes. This is Joel Perlmutter, and I voted no. A large part has to do with the rationale. I think this Alzheimer's treatment is a huge urgent unmet need, but I also think that if we approve something where the data is not strong, that we have a risk of delaying good treatment and effective treatment for more than a couple of years, for many years. I think there's a huge danger in approving something that turns out not to be effective. I think that danger is much, much greater. The other, all the individual components that we discussed raised questions that makes this not a strong study in my opinion. Thank you.

DR. FOUNTAIN: Okay.

DR. BONNER: Excuse me. Hello?

DR. FOUNTAIN: Yes?

DR. BONNER: This is LaToya, DFO. I want to restate the voting results for the record. So I
will restate the voting results: 1 yes; 8 nos; and
2 uncertain. I wanted to make that correction.

Thank you. You can proceed.

DR. FOUNTAIN: Thank you.

Next, Dr. Hoffmann?

DR. HOFFMANN: Yes. I voted uncertain, not
only because of everybody's comments, but I don't
really think the question was a reasonable request
of us because I don't see how you can ask us to
forget about something, that a study didn't happen
to make a decision on another study. It doesn't
seem fair, and I really can't view 302 in isolation
knowing about the existence of 301.

DR. FOUNTAIN: Okay.

Dr. Kryscio?

DR. KRYSCIO: Yes. Richard Kryscio. I
voted no for reasons specified earlier. Thank you.

DR. FOUNTAIN: Thank you.

Dr. Thambisetty?

DR. THAMBISETTY: I voted no mainly for the
reasons I specified earlier about dosing worsening
participants of the placebo arm, unblinding, and
the lack of appreciable minimal clinically important difference. Thank you.

DR. BONNER: Thank you.

Dr. Alexander?

DR. ALEXANDER: I voted no, and I would also just second I believe it was Dr. Perlmutter's comments. I think this is such an important application to get right because of the overwhelming imperative for new treatments and the precedent that's set, and what the application's review conveys to the scientific and clinical communities about the evidentiary thresholds for approval in this disease space.

There were I think six or seven reasons I voted no. The statistically significant effect was limited to the high dose, I believe, not the low dose. Forty percent of the ITT analysis didn't have the opportunity to complete week 78. There was no correlation with the biomarkers among the high-risk group if I understood recent comments, which is where the purported effect was demonstrated. Only statistically significant
effects were at the final endpoint, not at the
earlier endpoints or earlier time points I should
say.

The major stratum driving the findings up to
a third had a mid-study dose increase with more
potential unblinding. I'm not even sure if the
p-value is positive if revisited, but I'm going to
defer to Dr. Emerson on that one. Then the last
thing is the very modest effect. I also think that
the comments about minimally important clinical
difference were persuasive and informing my vote.

DR. FOUNTAIN: Thank you.

Dr. Onyike?

DR. ONYIKE: Chiadi Onyike. I voted no for
all the reasons that we heard in the discussion,
particularly comments made by Drs. Alexander,
Kesselheim, and Thambisetty. In addition, I
appreciate what Dr. Perlmutter had to say about
opportunity.

The one thing I would add is that in my
view, treatment effect is not just about achieving
a p-value. It's very much about the meaningfulness
of the effect size, and I think Dr. Thambisetty
spoke very eloquently about that. What I would add
to what he said is that the effect sizes as I see
them do not appear to lie outside of what you might
observe in the test-retest variability that you
might observe in ordinary clinical practice. Thank
you.

DR. FOUNTAIN: Thank you.

Next is Dr. Emerson.

DR. EMERSON: This is Scott Emerson. I
voted no. As I said before, I don't regard that
this could be regarded as a pivotal study. I do
very much appreciate the comments made by
Dr. Thambisetty, Dr. Alexander, and Dr. Onyike
about the clinical importance. This is the first
time I've heard an FDA person say that statistical
significance automatically was clinical importance.

I will say that if it were true, I did have
a tendency to extrapolate wildly at, say, a
25 percent decrease in progression, if you will and
might translate into a 33 percent increase in the
time to, although we never saw a responder analysis
or anything like that to help us differentiate those things. So that also was something that just meant that I couldn't say as much.

DR. FOUNTAIN: Okay. Thank you.

Dr. Jones?

DR. JONES: Yes. This is Dr. Dawndra Jones, and I voted no, and many of the reasons have already been discussed. I do believe, though, that this study did show some positive outcomes, but I can't really say that it was that strong study for all of the things we've already discussed. Thank you.

DR. FOUNTAIN: Alright. Thank you.

We can now move on to question 3, a discussion question. The primary evidence of effectiveness presented in support of aducanumab for the treatment of Alzheimer's disease is provided by Study 302. Study 103 is presented as supportive evidence of aducanumab's effectiveness. Discuss the evidence of effectiveness provided by Study 103.

I'd like to suggest that we accept the
wording of this and we just discuss the issue, unless someone has a specific way they'd like to get clarity on it.

Dr. Alexander, do you have a question about the wording or just a comment about it?

DR. ALEXANDER: Sorry. This is Caleb Alexander. Just a comment; I'm fine with the wording.

DR. FOUNTAIN: Okay. So let's just go ahead and discuss the question. I think we can agree on the wording.

DR. ALEXANDER: Right. Well, I just have a few brief comments here about Study 103, but I do think that it's one of these settings, as has been pointed, where it felt to me like the briefing materials really selectively identified lines of argument which would be supportive of 302, and then just sort of set aside a similar greater number of lines of argument that detract from 302.

So I understand that 103 was not designed to allow for prespecified efficacy analyses. I also was interested that the FDA's own biostatistical
reviewer noted that the efficacy analyses performed loose statistical significance after excluding individuals who were initiating concomitant medications for treatment of Alzheimer's disease.

The effect also in 103 -- [inaudible - audio gap].

DR. FOUNTAIN: I'm afraid we lost you there.

DR. ALEXANDER: -- and that of 302. I'm not sure if that's exactly right, but apparently the effect was tremendously larger. And contrary to 302, the effect was larger -- [inaudible].

DR. FOUNTAIN: I think we lost you again.

DR. ALEXANDER: I'm sorry. Can you hear me?

DR. FOUNTAIN: Now we can.

DR. ALEXANDER: Okay. So I was just concluding by saying that all of those points, the fact that it was not designed to allow for prespecified efficacy analyses; that statistical significance was lost after excluding those taking concomitant Alzheimer's meds; that the effect was 20 times larger than 302; and that also contrary to 302, the effect was larger in non-carriers than
carriers, all of those gave me pause. Thank you.

DR. FOUNTAIN: Thank you.

So there are two issues, one with the general concept of the difference between the statistical assessment here and in 302, and some of the concluding remarks from the agency. The second was specific to 103.

So maybe we could turn our attention for a moment to the FDA. I know this is the time for us to discuss it, but it's come up so many times, maybe we could ask the FDA, Dr. Dunn, or whoever he thinks is most appropriate, to comment on the difference between the statistical analysis and the overall conclusions about 103 as well as 302. Then while they're considering that, next up will be Dr. Gold after the FDA's comment.

DR. GOLD: So I'll wait for the FDA then.

DR. FOUNTAIN: Yes, if they're available.

DR. DUNN: Dr. Fountain, was that a statistical question? I couldn't quite follow the question.

DR. FOUNTAIN: Not exactly. So the question
is the statistical analysis done on 302, and in some degree on 103, brought up a lot of concerns about methods of analysis and so forth. And I wonder if you would like to comment on, or further comment on, the use of 302, for instance, without regard to 301.

DR. ALEXANDER: Do you mean 103?

Dr. Fountain, I'd be happy to try to sharpen my question. This is dr. Alexander.

DR. FOUNTAIN: Sure. That'd be good.

DR. ALEXANDER: Okay. I'd be interested, Dr. Dunn, or someone from the FDA, why do you believe that the effect was up to 20 times larger in 103 than 302? And why do you believe that contrary to 302, the effect was larger in non-carriers than carriers in 103?

DR. DUNN: Dr. Krudys, are you available?

DR. KRUDYS: Sure. I could take the second, the carriers versus non-carriers. The sample size for the treatment arms were about 30 to 40, so cutting into samples, subgroups, is going to be a pretty small sample size. So I'm not sure they
could get much from a subgroup analysis of a trial as small as Study 103 was, so I'm not sure going to the subgroups.

The first part of the question was what? I'm sorry.

DR. ALEXANDER: Why do you believe that the effect was up to 20 times larger in 103 than 302?

DR. KRUDYS: So there are some differences between the studies. The population is different. Study 103 was just in the U.S., and in Study 103 there's no titration to the 10 milligram per kilogram. They got it from the start and got consistent dosing of 10. So those are all things that can contribute to the difference between the treatment effect is Studies 103 and 302.

DR. ALEXANDER: Thank you.

DR. FOUNTAIN: Okay. Thank you.

Next is Dr. Gold, and I don't think we have to comment on every question, so maybe if it's something that you already agree with, you can just state your agreement.

DR. GOLD: No, I'll stipulate to the wording
of the question; it's not a problem. I'd just like to understand when the FDA talks about supportive evidence of effectiveness, is the FDA thinking that the effects on the CDR sum of boxes and mini-mental state in 103 are supportive despite the fact that it was not designed or powered for that?

In the same question that had been raised before that, there were other outcome measures in 103, presumably some of them more sensitive to changes in cognition that showed no effect. I'd like to understand how the FDA sees effectiveness in 103 when you have a kind of mixed sort of data.

DR. FOUNTAIN: Your question is, or your issue is, what constitutes supportive evidence of effectiveness?

DR. GOLD: Correct, particularly when the 103 study was not designed for efficacy, and B, when there are signals from other outcome measures that showed putatively more sensitive outcome measures but showed no effect.

DR. FOUNTAIN: Would you just like to make that as a statement for FDA to consider or would
you like to ask that as a direct question?

(Laughter.)

DR. GOLD: I'd like to ask a question.

DR. FOUNTAIN: Okay. We'll ask Dr. Krudys or who Dr. Dunn thinks is best suited, what constitutes supportive evidence of effectiveness?

DR. DUNN: Sure. I can take a crack at that. I think the main issue here was to try to -- and it seems to be causing a lot of consternation, and that's unfortunate. The issue here was actually to have attempted to provide clarity in the questions to reflect your ability to comment on the data in the way that it's presented in the briefing book.

So that was the intent. It wasn't intended to provide an artificial exclusion of any of the data, but in the context of the arguments that are made in the briefing book, to take it layer by layer. And we were hoping to get some insight from the committee, and I think we are, and we were listening hard. We were hoping to get some insight, kind of building up layer by layer in
terms of how these things go.

So the intent was to mirror the arguments in the briefing book that allowed 302 to be considered alone, for instance, for the artificial purposes of the first question, not as a way to ignore 301 but as a reflection of the arguments that were made in the briefing book about understanding the behavior of 301 in a way that was sufficient to facilitate the independent consideration of 302.

It was meant to kind of put the focus on if that were true. It was designed to try to get the focus on to what degree do you feel -- if one were reassured about what happened in 301, to what degree do you feel there's strength in 302? And I think indirectly to some degree you all have commented on some of that.

Similarly with regard to the 103 question, Dr. Gold, it's all in that context. So that's why the first part says primary evidence is in 302. I think it was well recognized throughout the document that 103 is a study of its character. We kind of mentioned that and certainly talked about
that.

In the setting -- again, for the purposes of
discussion, and that's why these are discussion
questions -- of if effectiveness in 302 exists, and
that's an if, then how does one think about 103?
Does that allow one to consider it as supportive
data in some fashion? And that's kind of a sliding
scale or some elasticity between that and how you
may or may not view the strength of 302.

So we were trying to get a little bit -- and
that's why these are discussions. We wanted them
to be an open dialogue about how you view any
evidence. Is it strong, is it weak, is it in
between? What's the character? We've heard some
comments about trying to subgroup out some of those
folks, and those are small subgroups and it's tough
to sort that out sometimes.

So the reason that those particular outcomes
take on relevance potentially is if the argument
about 302 that's made becomes relevant to the
consideration of 103, because those are the
outcomes that the study share. So it's just
designed to try to address those layers, peel them back a little bit individually before, as one of the committee members noticed, getting down to the bottom, and there's more integrated approach. So that was the intent. It was to just look at these relationships as cleanly as we could.

DR. GOLD: Thank you, Dr. Dunn.

DR. FOUNTAIN: I guess one of the important differences is before we talked about strong evidence. We're just saying here any supportive evidence. We're just saying here any supportive evidence.

I think Dr. Kesselheim is next.

DR. KESSELHEIM: Thank you. It's Dr. Aaron Kesselheim. I share the concern raised by Dr. Gold. I also wanted to raise the point that it is challenging to ask us to identify supportive evidence for a trial in 302 that's already of questionable strength in a trial like 103 that was not designed to provide supportive evidence but was designed for evaluation of other things of which the efficacy measurements were a supplementary or secondary component of that analysis.
As a result, I think that's why you're getting in 103 efficacy results that seem very discordant from the efficacy results that you see in 302, in addition to the fact that the efficacy results are observed over the course of a 54-week study, whereas in figure 5 of the FDA documents, there doesn't appear to be any effect of the high-dose group at 50 weeks of analysis.

So there is discordance not only in the level of the effect size, but in the timing of the effect and of the dosing as was mentioned. And all that stuff makes it very hard to try to bolster something that already needs real bolstering.

Then also by the way, to skip over 301 -- because, again, the way that you try to bolster a study like 302 is by looking at another well-designed similar study, but that other study which is 301, which, again, we're not supposed to be talking about in this context of this question, is a negative study. So for me, I think for those reasons, Study 103 provides minimal support.

DR. DUNN: Thanks, Dr. Kesselheim. Can I
ask you to comment on the points that were made about the relationship between the 0- to 54-week dosing in 103 and the 26- to 78-week dosing in 302, 301 and 302? Can you tell me your thoughts about that, please?

DR. KESSELHEIM: I guess what I was specifically saying is that it looks like that the effect was observed here in 103 after 54 weeks of treatment, whereas it doesn't appear that in 302 there was any effect at all observed in the high-dose group.

DR. DUNN: Yes, sir. I was wondering if you could actually speak to the points that we made in the briefing package about that issue.

DR. KESSELHEIM: Yeah-yeah. Again, I think that that's just more -- the fact that these are -- and I appreciate that you brought that up, but I'm just talking about the fact that I think that that's just more lack of alignment between the two studies that makes it hard to provide direct support for it in my mind.

DR. DUNN: Okay. I'm sorry. Let me be a
little more direct. There were some points made in
the briefing book about the fact that the
equivalent time period to compare in 301 and 302 to
103 is the 26- to 78-week window. There's a
titration period involved in Studies 301 and 302,
and the briefing package made a point to say that
the relevant time period of comparison between
0 and 54 in 103 is 26 to 78 in 301 and 302 because
of the absence of titration in the 10-milligram
group in 103. I was just wondering if you had
noted that or had any thoughts about that.

DR. KESSELHEIM: I did. I appreciate that.
The titrating patients still received that
additional therapy and it was still part of the of
the trajectory of their care, and I appreciate that
you pointed that out. But again, it just speaks to
the differing organizations of the two trials.

DR. DUNN: Okay. I understand your point
now. Thank you.

DR. KESSELHEIM: Thank you.

DR. FOUNTAIN: Okay.

We'll move to Dr. Kryscio, if you still have
a comment.

DR. KRYSCIO: Yes. I was just saying that I think that 103 informed the design of 302 from the point of view of determining a desired effect size when they basically determined their N to attain the power they were looking for. Obviously, the study was truncated; that is 302 and 301 were both truncated, so therefore they had a bit of a problem. And as it turned out, the effect size that was seen in 302 was much smaller, I'm sure, than what was derived from when they designed a study using the data from 103.

So therefore what happens is a very simple explanation. 301 got to be positive, yes -- or 302 got to be positive, but 301 did not. It's just a simple statistical power issue. They're getting a smaller effect size than what they had planned on using the data in 103.

DR. DUNN: Dr. Kryscio, thank you for that.

I think I might like to ask the applicant to comment on that. I don't have precise numbers at my fingertips, but I believe the applicant has
informed us that, actually, they powered their
study for an effect size very similar to what they
observed. I might be wrong about that, and if I
am, I apologize. But could we have the applicant
comment on that, please?

DR. HAEBERLEIN: Yes, that's correct. We
powered the study for a 25 percent change from
placebo at week 78, so very close to the 22
percent.

DR. FOUNTAIN: Okay. Thank you.

DR. KRYSCIO: Yes. It's Kryscio again.
Yes, but you only got to run two-thirds of the
study, so that clearly affects the power.

DR. HAEBERLEIN: I'm sorry. Was that
question to me? The 22 percent did have a
statistically significant outcome.

DR. KRYSCIO: Yes, but you two underpowered
studies, one in which is positive and one in which
just didn't work out.

DR. HAEBERLEIN: In the study that was
positive, the less data obviously makes it more
difficult to achieve that statistical significance,
but nonetheless you did still have statistical significance. In the study that was not positive, as you've seen in the briefing book, we've understood what differentially impacted that study.

DR. FOUNTAIN: I think I'd agree with you, Dr. Kryscio. To make a comment, what you're suggesting is if you enrolled enough patients, then they would have had enough power to find a difference potentially. Is that right?

DR. KRYSCIO: That's what I'm bringing up, yes.

DR. FOUNTAIN: I think that's the way I would view it.

So let's move on here to Dr. Emerson. Maybe I could make a comment or question first.

I'm having a lot of trouble with the details because in the big picture, for instance 302 being positive and being statistically significant, it's a small difference and there's a lot of other details. But fundamentally if you look at 103 in its final analysis, there's statistical significance that's seemingly meaningful at the
10-milligram per kilogram dose, and it's across subgroups, and same for 302.

So I'm having trouble understanding why 302 should be so thoroughly rejected if it's positive. I understand why 301 would be rejected, but I'm having trouble understanding 302, and it seems to be 103, because it looks in the same direction as 302 and would support 302. So I understand why there's no question 301 is negative. That's not even an issue. But it seems to me there's no question 302 is positive and that 103 found a difference at the 10-milligram per kilogram dose, which would support it.

So I'm having a lot of trouble understanding why. Maybe Dr. Emerson who's coming up next, and I think commented on this, could help me understand that.

DR. EMERSON: Yes. This is exactly the point that I wanted to make. 103 was a preliminary screening trial. Had it been completely negative, 301 and 302 would have never been done. Phase 2 studies are always positive in some way, and what's
nice about 103 in this particular case is I viewed the modifications to the eligibility criteria and what else they were doing as relatively slight. There are other times where you're chasing after subgroups and you're just saying it's there, but every phase 2 study is so impossibly biased in its treatment effect that you should never be surprised when you get less result in the confirmatory study. Because of that, I gained some solace from 103. The thing that bothered me the most is, again, due to pressures of time -- and, again, this is a direct complaint -- and so much time spent telling me things were excessively understood and very persuasive and not enough time looking at the data, I never got to really delve into what the problems were with the randomization schemes and direct comparisons, and particularly direct comparisons by randomization comparison superimposed on the 302 results before I'd believe it was very supportive.

So there is something to be gained. If you told me you had 302 with no phase 2 study, I'd say,
"Great. Give me two more confirmatory studies," but in no sense would I regard that 103 is going to be the place of another confirmatory study. That doesn't make me relax criteria for what would regard 302 as pivotal. And just note that an underpowered study decreases the positive predictive value of a positive result. Lots of people go, "Well, yeah, it was a small study but the effect was huge." Well, they've got cause and effect wrong.

In order for a small study to be statistically significant, it has to have a huge effect. It has to or it won't happen, but that doesn't mean it's correct. And by the time you say we're not taking all results, we're only taking it when it's positive, it's a very, very biased result.

So the positive predictive value, we don't just want to worry about the type 1 error which says make certain we don't approve distilled water and the sponsor wants to say if we have an effective drug, it really works. That's the power.
But we are concerned with the Bayesian positive predictive value, and in an underpowered study, and one in which you let the type 1 error creep up, it's very low.

This is the reason why confirmatory studies, depending upon the diseased area and depending upon how much we know about it, anywhere between 20 percent and 70 percent of phase 3 studies confirm the phase 2 results, and it has to do with that positive predictive value.

DR. FOUNTAIN: Okay. That's very clear. Thank you. I didn't mean to cut you off. I just want to say you answered the question that I had, and it was clear. But if you have another point, please make it.

DR. EMERSON: That was it.

DR. FOUNTAIN: Okay. Great.

Let's see. In terms of the discussion of the question, I think Dr. Perlmutter is next if you still have a question or comment.

DR. PERLMUTTER: I do. I just want to point out that I would say 103 does not support 302, and
that is the high dose. 103 initially looked like it was 0.04, but then after you exclude those who had concomitant AD meds, it was 0.095. So there's no direct support there.

DR. FOUNTAIN: Let's see. Dr. Emerson, you still have your hand up, and Dr. Perlmutter should put it down unless you have a question. Then Dr. Thambisetty, I see you have your hand up as well.

DR. THAMBISETTY: Thank you, Dr. Fountain.

DR. FOUNTAIN: Do you have a comment to make?

DR. THAMBISETTY: Yes, please.

There were a couple of things that set Study 103 apart. Unlike Studies 301 and 302, the applicant actually has made data and results from Study 103 available for independent peer review, and these findings were published in 2016 in Nature. I think it's really important to quote directly from the Nature paper about the appropriateness of using these data to make decisions about clinical efficacy, so let me quote
directly from the Nature paper.

Quote, "The trial was not powered for exploratory clinical endpoints. Thus, the clinical cognitive results should be interpreted with caution. Primary analyses were based on observed data with no imputation for missing values. Nominal p-values were presented with no adjustments for multiple comparisons," end quote.

So I think it's worth remembering, yet again, that this was a safety and tolerability study. There were five purely exploratory clinical endpoints that were analyzed. In addition to the CDR sum of box scores and MMSE that we are now considering, there were three other tests, the Neuropsychiatric Test Battery; the Free and Cued Selective Reminding Test; and the Cognitive Drug Research Computerized Test Battery, which we are not discussing in any detail, and they're completely I think ignored in the briefing documents that we have.

The other quick point that I'd like to make is there also does not appear to be a strong
dose-response effect in Study 103. I can give you one example. In tables 25 and 26 of the briefing document, using an ANCOVA model, the magnitude of change in MMSE scores in 3 milligram versus placebo comparison is 1.7 MMSE points, and this is at a raw unadjusted p-value of 0.07. This is more than 3-fold higher than in the 6-milligram per kilogram comparison with placebo, which is with the raw unadjusted p-value of 0.61.

Moreover, these results seem to be attenuated in the MMRM model, so not only do we have an issue with using purely exploratory clinical endpoints, we also have an issue with a small study that seems to show really unstable effects that are not very robust to adjustment with covariates. Thank you.

DR. FOUNTAIN: Okay. I guess that's reflected in the FDA slide presentation we saw today on slide 33, which listed the outcomes by dose, which look like a dose response. But what you're saying is, first, that only the final 10-milligram per kilogram dose was statistically
significant at 0.04, and for the CDR sum of boxes and for the MMSE, at 0.03. But you're saying if that's corrected beyond the ANCOVA model that was used here, that p numbers become even worse and not significant. So you wouldn't think there is dose response for clinical outcomes in 103.

Is that a summary?

DR. THAMBISSETTY: Yes, and also the 3-milligram per kilogram dose seems to have a warping effect on MMSE compared to the 6-milligram per kilogram dose, which again goes against a dose-response effect. So the 3-milligram per kilogram dose --

DR. FOUNTAIN: Small --

(Crosstalk.)

DR. FOUNTAIN: Right. Okay.

So maybe we should move to vote 4. It looks like we've addressed this, and everyone's questions have been answered, and we seem to have a lot of consensus discussion on this. So let's move to number 4. Does Study 103 provide supportive evidence of the effectiveness of aducanumab for the
treatment of Alzheimer's disease? Yes, no, or uncertain.

DR. ALEXANDER: So can I ask a question about the language here? This is Caleb Alexander.

DR. FOUNTAIN: Sure.

DR. ALEXANDER: This is Caleb Alexander. I have a little bit of concern about the language. I guess I'm wondering is there also a question after this that is worded, "Does Study 103 provide supportive evidence of the ineffectiveness of aducanumab for the treatment of Alzheimer's disease?"

In other words, it seems to me this is a great emblematic example of a lot of the briefing materials that were provided that, it seemed to me, selectively used lines of evidence from 103 and 301 to support the findings of 302 at the expense of calling out any number of lines of evidence that call into question the findings of 302. Thank you.

DR. FOUNTAIN: I think we're asked the question here. I think we'll have to ask Dr. Dunn to elaborate on that, but I understood Dr. Dunn to
say that in their briefing materials, they presented this discussion and they wanted us to address it. So one of the supportive lines of evidence for the effectiveness of aducanumab could come from 103, and they're asking us if we think that's true or not or uncertain. And I guess it'd be no if it was ineffective.

DR. ALEXANDER: Well, let me just say -- this is Caleb Alexander again -- having spent a lot of time doing survey work, I would suggest a question that asks whether we believe the evidence supports effectiveness, ineffectiveness, or both would be a more balanced way to approach this. I'm not suggesting that the question be rewritten at this point, but I'm just registering my concern about the wording of the question.

Thank you.

DR. DUNN: Dr. Alexander, can I just ask you -- I appreciate what you're saying. I think the intent here was to get a sense by allowing as many options as possible on the questions and was just to recognize that the application presents 302
as primary evidence and presents 103 as supportive evidence.

Under the rubric that 302 represents interpretable evidence of effectiveness, then I'd like to think we did a pretty good job talking about the limitations of Study 103. We've talked about some of them here in this discussion, that it's a small, early-phase trial, and all the things we discussed. And I think the intent was to try to tease out that with those limitations of that study, does it contextually provide any support whatsoever to 302.

That does obviously build upon how you may think about 302. That's why we didn't make the question contingent on any particular interpretation. If you don't think 302 is worth anything, then of course 103 may not support anything. It's supposed to be a contextualized question.

When you say does it provide evidence of ineffectiveness, what does that look like to you? What would that look like to you conceptually?
DR. ALEXANDER: Hi. This is Caleb Alexander. We just had a lengthy discussion about the various reasons for concern in using 103 to support 302, and frankly I think a lot of those will come out in the explanations of our answers to this question. So again, I don't mean to provide an unnecessary speed bump here.

DR. DUNN: No, no --

DR. ALEXANDER: I'm just calling out the fact that this question is, in my mind, open to, again, eliciting selective information, and I just want to be sure that the sponsor and that you, the FDA, get as much value as you can from the advisory committee that's taking place.

DR. DUNN: Yes, absolutely, Dr. Alexander. I understand completely. I think what we're hoping for is that you have the answer available to you.

Let me just ask one clarifying question, which really should help me. Are you using evidence of ineffectiveness synonymously with a lack of evidence of effectiveness, like a complete absence of that? Is that what you mean by that?
DR. ALEXANDER: No. No. I view evidence of ineffectiveness as different from evidence of a lack of effectiveness. Thank you.

DR. DUNN: Thank you.

DR. FOUNTAIN: I guess that's maybe where we should have started this whole discussion is with the rubric. So I think that the rubric starts with trying to figure out if 302 is positive or not, and then if it's positive, goes down these other avenues, because if it's negative, you don't go very far.

If we take this question in isolation, does Study 103 provide supportive evidence of the effectiveness of aducanumab for the treatment of Alzheimer's disease, it's in the rubric that you're considering there is some evidence somewhere of effectiveness for aducanumab, I suppose. But I think you're right. It's most important in answers to the voter, the discussion we've already had, really.

If there are no more comments -- Dr. Thambisetty, do you have another
comment about this or is your hand still raised
from last time maybe?

DR. THAMBISETTY: I'm sorry. No, I don't
have any other comments.

DR. FOUNTAIN: Okay.

So if we don't have any other comments or
questions, we can move to begin voting on question
4.

DR. BONNER: We will now move voting members
to the voting breakout room for vote only. There
will be no discussion in the voting breakout room.

(Voting.)

DR. BONNER: For the record, the vote
results are displayed, zero yes, 7 nos,
4 uncertain. I will now turn the meeting back
over to the chair.

DR. FOUNTAIN: Thank you. We'll now go down
the list and have everyone who voted state their
name and vote into the record. You may also
provide justification of your vote if you wish, and
we'll start with Dr. Kesselheim.

DR. KESSELHEIM: Thank you. This is
Dr. Kesselheim. I voted no. Following Dr. Fountain's rubric, since I don't think that 302 provides solid evidence of the effectiveness of the drug, it's challenging for me to also think that Study 103 provides supportive evidence.

I think that if there was a very solid trial that was supporting the evidence of the drug, that a phase 1-2 like this could provide supportive evidence. But since there isn't that, in my mind I don't think that this is able to do that, in part because of some of the methodological differences that Dr. Dunn and I were talking about and that he helpfully pointed out. But in general, just because the study wasn't designed to gather evidence of effectiveness as its primary goal, that's why I voted no.

DR. FOUNTAIN: Okay. Dr. Onyike?

DR. ONYIKE: This is Chiadi Onyike. I voted no. I'll let the record speak for me, but in particular I would highlight what Dr. Thambisetty and Dr. Emerson said. Thank you.

DR. FOUNTAIN: Dr. Duda?
DR. DUDA: This is Dr. John Duda. I also voted no for the same reasons, the limitations of the phase 2 aspect, the design differences, and the other statistical considerations that were brought up.

DR. FOUNTAIN: Thank you.

Dr. Alexander?

DR. ALEXANDER: I said I was uncertain. The reasons why I would have concerns about using 103 to support 302, including that 103 wasn't designed to allow for prespecified efficacy analyses, the efficacy lost statistical significance after excluding those with concomitant Alzheimer's medicines. The effect was 20 times larger, if I understood correctly, than that of Study 302. I know that there were small sample sizes, but contrary to 302, the effect was larger in non-carriers than carriers.

Then the last two points that have been pointed out, one, some highly sensitive measures did not reach statistical significance. Then finally, as was recently mentioned I think by
Dr. Thambisetty, there was a lack of a strong
dose-response relationship.

DR. FOUNTAIN: Thank you.

Dr. Hoffmann?

DR. HOFFMANN: I voted uncertain because of
some of the same reasons everybody else has. It
asked is it supportive of a given study and yet we
don't know what study to use. We can't really view
302 in isolation. This was a phase 2 exploratory
study. It was much smaller. It only used two
efficacy scales versus six as in the other larger
studies. And for all of those reasons, I voted
uncertain. Thank you.

DR. FOUNTAIN: Thank you.

Dr. Kryscio?

DR. KRYSCIO: It's Richard Kryscio. I voted
no for reasons already stated.

DR. FOUNTAIN: Dr. Thambisetty?

DR. THAMBISETTY: Yes. I voted no because
Study 103 remains a phase 1B safety and
tolerability study and should only be interpreted
as such. It was not powered to assess clinical
endpoints. Thank you.

DR. FOUNTAIN: Thank you.

Dr. Perlmutter?

DR. PERLMUTTER: This is Joel Perlmutter, and I voted no for the reasons already stated.

DR. FOUNTAIN: Thank you.

Next is me, Nathan Fountain. I voted uncertain because I do think there's some evidence of effectiveness. There's what I would view to be the trend of a dose response in the PET SUV measurements and in the two limited measures used. But on the other hand, it's not powered or intended for this purpose, so for all the other reasons stated, I said uncertain.

Dr. Emerson?

DR. EMERSON: This is Scott Emerson. I voted no. On Study 103, the positivity or any evidence it has is a prerequisite for the other clinical trials but just for added emphasis. In no way would I be accepting regarding this as an adequate and well-controlled trial to make it two there. We need confirmatory studies. So again,
302 as a pivotal study or 302 and 301 as two confirmatory studies are there, but 103 cannot take the place of another confirmatory study.

DR. FOUNTAIN: Dr. Jones?

DR. JONES: Yes. This is Dr. Dawndra Jones, and I voted uncertain. I agreed with you, Dr. Fountain. I saw some positive look in effectiveness, but based off of the study design, truly unable to really decide, to make a decision if there's truly that strong effectiveness that we're looking for in this study.

DR. FOUNTAIN: Thank you.

We'll now move to point 5, which is a discussion question. The application presents evidence in support of effects on the pathological hallmarks of Alzheimer's disease, including effects on amyloid beta, tau, and downstream markers of neurodegeneration, using multiple assessment modalities. Discuss the impact of these results.

In my mind that's a little bit of a two-part question. First is what you think of all those markers and how they were assessed, and second,
what is the significance of those markers? You might interpret it differently. That's how I would interpret that question.

First, let's open it up for other interpretations or questions on the wording.

Dr. Hoffmann, you may have your hand up from last time.

DR. HOFFMANN: Not really on the wording, but on the concept. I think aducanumab did show a demonstrable effect on amyloid, hopefully, the exact species, which we don't know which is the toxic species yet and could be one concern.

Also, in a smaller number, people were shown to reduce tau as a downstream indicator, but in several studies that I've reviewed, in fact recently in JAMA Neurology, in June there was an extensive study out of the University of Kentucky Alzheimer's disease department that showed over 69 percent of the patients who died of dementia. In their autopsies it showed multiple proteinopathies, including beta-amyloid and tau, but also alpha-synuclein and another DNA-related
drug. I think it's called TDP-43.

I think one of the problems we have with all these neurodegenerative agents is we'll target one or two of the epitopes that we're looking at to modulate the neuron loss, but we don't really know all of the proteinopathies that are taking place until the person dies. So even in this study, I believe a big portion of those discordant results could have been mixed pathologies that we're totally unaware of in the patient groups between 301 and 302, so I think we should take that into consideration. We just don't know. It may have a good effect on amyloid beta and tau, but what about all these other misfolded proteins that could be present that we won't know and we can't identify now at least until autopsy?

DR. FOUNTAIN: Okay.

Dr. Thambisetty?

DR. THAMBISETTY: Thanks, Dr. Fountain.

I think from the results published from 103 as well as with 301 and 302, there's clear evidence from brain amyloid PET imaging that aducanumab dose
dependently clears amyloid plaque from the brain.
I think that's pretty compelling. The drug appears to generate precisely the neuroimaging biomarker that you would expect by virtue of target engagement. I don't think there's any doubt about that in my mind.

But in the larger context of the discussion today, particularly with relevance to the impact of aducanumab and slowing some of disease progression, the question is whether lowering of brain amyloid burden as evidenced by PET imaging results in a clinical benefit. I think those are very distinct questions, but I think one follows the other very logically.

With regard to this question, I think the data are far less compelling. I would point to slide 20 of the FDA statistical reviewer's presentation, where you examine the relationship between change in global brain amyloid burden at week 78 in individuals exposed to high-dose aducanumab and change in the CDR sum of box scores. There really appears to be no relationship either
in Study 302 or 301, and this appears to be the case even when the analysis is restricted to only individuals exposed to the 10-mg per kilogram dose.

I think there are some larger implications of these findings which we are not tasked with discussing today. One of the larger questions relevant to these observations is whether lowering brain amyloid burden is in fact the correct target in Alzheimer's disease, but like I said, I think that's beyond the remit of the discussion today.

Thank you.

DR. FOUNTAIN: Okay.

So it looks like we're going to be relatively short on time, so in this question in particular we might be able to group our answers. Let's see if we can try to consolidate them a bit.

I think next up is Dr. Duda.

DR. DUDA: I in that vein agreed that I think the evidence is fairly compelling that there's an effect on AB in the brain. A number of us are having difficulty with the lack of an association between the CDR-SB and the PET imaging.
I think it would be very helpful if the statistician and the other members of the FDA team had come together and tried to understand the discrepancy between the two analyses. If it really was just a ceiling effect or a power problem, why was one analysis suggesting a correlation and another not? I think that directly impacts on how I feel about the impact of that finding.

DR. FOUNTAIN: Okay. That's understandable.

Dr. Gold?

DR. GOLD: Hi. I just wanted to say that at least one of the things that we got excited about when we saw the 103 study when it first came out was there was unequivocal evidence of target engagement, so this was remarkably positive data. It was clear that there's a dose proportional response. In some of that we see both.

I'm looking at the clinical reviewer's graphs in the briefing document. That's been replicated in the study, albeit in subgroups. Where I'm having more issues in terms of the actual downstream biomarkers is the effect actually on tau
because that's really what we believe drives the neurodegeneration.

So the effect on tau are not quite as clear, partially because it's tiny sample sizes. And I understand that subjects in studies may not like to have lumbar punctures, so that limits the amount of data that we can collect.

The part that I'm struggling with also is when we actually look at the effect on tau using PET, that although there's an effect in reducing tau, the vast majority of the data on tau effect comes from the 301 study. So 31 out of 37 subjects come out of the 301 study and presumably that's where you're seeing downstream effects on tau. So it appears that there's an effect on the downstream biomarker, but if you believe it, it's just disconnected from a clinical effect.

DR. FOUNTAIN: Okay. Yes, I think that's been mentioned before as well.

Let's take one more comment and then vote, because in the vote also we have an opportunity to state it. And I think Dr. Kesselheim is next.
DR. KESSELHEIM: This is Dr. Kesselheim. I don't want to take too long. I just wanted to applaud, in a sense, Biogen and the FDA here for not simply resting on the effect of this drug on the biomarkers because the effect of the biomarker does seem pretty significant, but then actually going on and doing the tests necessary to evaluate the clinical effects of the drug and leading to the discussion that we're having today.

Other than that, I think that what Dr. Thambisetty and Dr. Gold said about those biomarkers is right. We need to make sure that if we are going to rely on biomarkers, that they are well validated with their clinical endpoints.

DR. FOUNTAIN: Yes, I'd agree with that as well, for my two cents.

I think we could probably move to the voting now, and that will also give everyone an opportunity to comment on this.

DR. PERLMUTTER: I'd like to comment. Can I make a comment? This is Joel Perlmutter.

DR. FOUNTAIN: Who is that? I'm sorry.
DR. PERLMUTTER:  Joel Perlmutter.

DR. FOUNTAIN:  Okay.  If you have a brief comment, that'd be great.

DR. PERLMUTTER:  Yes.  I'm kind of a world expert on PET imaging.

DR. FOUNTAIN:  Right.

DR. PERLMUTTER:  So I'd think it would be relevant.

I think, first of all, the comments about the relationship of target engagement I think is totally appropriate, but the disconnect or the lack of correlation with the clinical benefit is a real problem.

The second thing, that tau imaging was done on a non-randomized group and we have also a huge issue of off-target binding with the tau imaging agent.  So I don't think that really provides us any specific information in this particular case.  I think the idea of going after these is terrific and trying to find target is great, but whether that's the right target or not, that's a bigger issue that came up earlier, and I agree that's a
major problem. Thank you.

DR. FOUNTAIN: Okay.

Let's move to the voting, and of course you'll have an opportunity during the voting to discuss this as well.

DR. BONNER: Dr. Fountain, can we summarize the discussion for question 5 please before we proceed forward?

DR. FOUNTAIN: Yes. So the discussion is that it seems as though there's evaluation of several of the biomarkers listed here, and while there's some evidence that they trend in the right direction, because they don't co-trend entirely, or sometimes at all, with the clinical outcome, there's some concern about their value in supporting it. But I think the overall impression is that it supports some of the pathological hallmarks of Alzheimer's disease, but there's a lot of individual considerations for each of the biomarkers with variable opinions about the degree of confidence.

Okay. So now we can move to the voting
question, which parallels the discussion question. Has the applicant presented strong evidence of a pharmacodynamic effect on Alzheimer's disease pathology? Yes, no, or uncertain. Any discussion on the wording before moving to the vote?

DR. THAMBISETTY: I have one comment on the wording.

DR. FOUNTAIN: Just before you begin, if we could have everyone raise your hand if you have a comment on the wording; otherwise, you could maybe look and make sure your hand is unraised.

Was that Dr. Thambisetty?

DR. THAMBISETTY: Yes, Dr. Fountain, if I may?

DR. FOUNTAIN: Yes.

DR. THAMBISETTY: I want to clarify whether or not this question includes effects of the biomarkers related to brain pathology as well as reading out clinical effectiveness because those are two completely different questions. I want to be sure I understand that the question is capturing one or the other, or both in this.
DR. FOUNTAIN: I think understand the question, and I think we can ask the FDA if we're undecided, but I think we get to decide that. And I think the question crosses anything you think might be pharmacodynamic mostly related to what I would call biomarkers that we talked about in the discussion.

DR. THAMBISETTY: If I think that there's good biomarker evidence for brain pathology but not good biomarker evidence for clinical efficacy, how would I vote on this question?

DR. FOUNTAIN: You'll have to decide for yourself if that constitutes strong evidence of a pharmacodynamic effect on Alzheimer's disease pathophysiology.

DR. THAMBISETTY: Got you. So you think the term "pathophysiology" would also include treatment effects and therapeutic efficacy?

DR. DUNN: Dr. Fountain, you may intentionally be not wanting me to clarify --

DR. FOUNTAIN: No --

DR. DUNN: -- in order to --
(Crosstalk.)

DR. FOUNTAIN: -- that would be great if you'd clarify.

DR. DUNN: Okay. It's always interesting to work on questions hard and then see how people read them. This question was absolutely intended to represent the biomarker-based assessment of the pathology of Alzheimer's. Really, we're talking about amyloid and tau, and there was also obviously some downstream effects, not specifically. But that's what we're talking about here, mainly amyloid. But it's not a clinical meaningful question. It's about what effect has been demonstrated using the biomarkers that we have on the pathophysiological findings.

DR. THAMBISETTY: Got you. So no relation whatsoever to clinical effectiveness and the biomarker profile.

DR. DUNN: Yes. I'm wondering maybe if the word "strong" is what's got you thinking that.

DR. THAMBISETTY: Exactly. Exactly.

DR. DUNN: Yes. That's really meant to
speak to the evidence on the marker itself. So you can probably pretty easily envision a marker that has -- in the abstract, a random drug might have some of what you might think of as weak evidence on a marker, and this is really meant to get at the type of thing that Dr. Gold was commenting on before, and I think you were as well.

DR. THAMBISETTY: Great, because we know that PET imaging of amyloid does in fact measure amyloid, but that's not the question that we're being asked.

DR. DUNN: Yes. We're --

DR. ALEXANDER: I'm sorry. This is Caleb Alexander.

Dr. Dunn, is another way of asking this simply asking has the applicant presented strong evidence that the product modifies biomarker parameters of Alzheimer's disease, such as amyloid plaques, and tangles, and tau, and stuff like that?

DR. DUNN: I think for the purposes that you're asking it, Dr. Alexander, that's probably okay, yes. That's not how I would word, but yes, I
think that's --

DR. ALEXANDER: I know that was a bit verbose or not so eloquent, but the bottom line is you're getting at whether we believe that the product does or does not -- is there strong evidence that the product has an effect on these pathophysiologic measures of Alzheimer's disease.

DR. DUNN: That's right.

DR. FOUNTAIN: Okay. So that clarifies it I think as much as we can.

Dr. Kryscio, I see you put your hand down. I don't know if you still have a question.

DR. KRYSCIO: No. I'll cover it in the comments on my vote.

DR. FOUNTAIN: Okay. So I think we can move to the vote then.

DR. BONNER: For the record, LaToya Bonner. We will now move voting members to the voting breakout room to vote only. There will be no discussions in the breakout room.

(Voting.)

DR. BONNER: LaToya Bonner. For the record,
results displayed for vote question 6, 7 yeses; 6
uncertains; zero nos.

I will now turn the meeting over to the
chair.

DR. FOUNTAIN: Thank you. We will now go
down the list and have everyone who voted state
their name and vote into the record. You may also
provide justification of your vote if you wish, and
we'll start with Dr. Kesselheim.

DR. KESSELHEIM: Thanks. This is
Dr. Kesselheim. I'm not sure why I keep going
first. Maybe it's the two A's in my first name.
But I voted uncertain because while it is very
clear that the drug provides substantial impact on
the biomarkers that it measured, because the effect
of the changes in those biomarkers on the clinical
impact of the drug is unclear, that left me
uncertain as to whether or not it had an impact on
Alzheimer's disease pathophysiology. Thank you.

DR. FOUNTAIN: Thank you.

DR. Onyike?

DR. ONYIKE: Yes. This is Chiadi Onyike. I
voted yes. I viewed the question narrowly. This is a treatment designed to basically [indiscernible] out amyloid pathology, so I view the question as did it actually do that. There's clear evidence that it did that in a dose-related fashion.

There is some ambiguity, as Dr. Gold and perhaps others discussed, regarding downstream effects on tau, but fundamentally this compound is not designed, at least in the pharmacodynamic sense, to alter tau pathology -- to engage with tau pathology. It's specifically designed to directly engage with amyloid pathology, and it did that. Thank you.

DR. FOUNTAIN: Thank you.

Dr. Duda?

DR. DUDA: This is John Duda. I voted yes because I do believe there's strong evidence of a pharmacodynamic effect on Alzheimer disease pathology, specifically amyloid pathology, and in my mind that justified a yes. Thanks.

DR. FOUNTAIN: Thank you.
Dr. Hoffmann?

DR. HOFFMANN: Yes. I voted yes, but primarily because it was mentioned that we were just talking about amyloid beta and tau. But again I'd like to point out that I think there are a number of other proteins that are misfolded that could be involved in Alzheimer's that we really don't understand yet. I think that's the reason why you didn't see super excellent results with this drug because if it was targeting all the toxic species, I think we would have seen much better efficacy results. Thank you.

DR. FOUNTAIN: Thank you.

Dr. Jones?

DR. JONES: Yes. This is Dawndra Jones. I voted yes because I believed it clearly demonstrated positive impact on the biomarkers, especially concerning the amyloid pathology. Thank you.

DR. FOUNTAIN: Dr. Perlmutter?

DR. PERLMUTTER: Well, I said uncertain, and I agree with everybody actually. I think there's
no question it demonstrates engagement with the
A-beta amyloid. I think the tau is very uncertain.
The question in my mind is whether that's the
correct biomarker to use for the relevant clinical
effect.

DR. FOUNTAIN: Thank you.

Dr. Alexander?

DR. ALEXANDER: I voted uncertain. I just
want to say as an aside, because it's the last time
that I may speak, both to thank sponsors and the
FDA for the enormous amount of work that you put
into making today possible. I also want to just
note that the briefing packet was unique in that it
was co-produced, and I do think there's some merit
in having separate packets produced by both
parties, or at a minimum having the FDA provide the
briefing materials and having the sponsor add their
commentary to the FDA's review rather than vice
versa, given the FDA's role as regulator here.

Regarding this question at hand, I think it
is, as was noted, important to note that the
absence of correlation between the reduction in
amyloid and clinical efficacy, at least among the high-dose group, I do think there's very good evidence that the product reduces amyloid. But as was noted, the impact on tau was more difficult to understand the meaning of that because it was among what I understand to be a selected or non-random subset. Thank you.

DR. FOUNTAIN: Thank you.

Dr. Emerson?

DR. EMERSON: I tended to answer this narrowly as did Dr. Onyike. The pathophysiology of Alzheimer's include signs of amyloid deposits. I think this has affected that. Whether it has affected symptoms or clinical sequelae that matter more is unclear, but in the sense that something has changed, I said yes.

DR. FOUNTAIN: Thank you.

Dr. Thambisetty?

DR. THAMBISETTY: I voted uncertain because while I think the biomarker profile in terms of amyloid is very elegant and compelling, it becomes a little bit murky in terms of tau, so I think the
sample size is rather small. There's considerable heterogeneity in baseline power levels that we know from previous studies, and tau PET, again, is a fairly novel imaging modality that hasn't been fully validated in very large cohorts. So for those reasons, I voted uncertain.

DR. FOUNTAIN: I'm next, Nathan Fountain. I voted uncertain because I think there is evidence. I'm not sure how strong it is, though, but I do think there's evidence.

Next is Dr. Kryscio.

DR. KRYSCIO: Yes. I voted uncertain because I guess I'm at a neuropathology center, and it's not a hundred percent clear what's measured by PET; it's actually what is measured at autopsy. Of course I agree that the evidence for tau is very low here.

I'd also like to add, because it was discussed before, the other proteinopathies, which is TDP-43 and alpha-synuclein. I don't know if they're really issues in this particular case. They certainly could contribute to the reasons why
people get a clinical diagnosis of dementia, but that usually occurs when you're over 80, and the people in this study were in their 70s. So I'm not so sure that plays a big role in this particular case.

DR. FOUNTAIN: Thank you.

Alright. We'll now move on to number 7, which is a discussion question.

Study 301 was a negative study. Post hoc exploratory analyses were conducted in order to achieve maximum understanding of the partially discordant results of Studies 301 and Study 30, and to determine if this understanding precludes independent consideration of Study 302.

Additional contribution to the understanding of aducanumab's pharmacological activity and clinical effects is provided by the results of Study 103. In light of the exploratory analyses that were conducted and the results of Study 103, discuss the impact of the results of Study 301 on the consideration of the results of Study 302.

If I might start the discussion by saying
we've pretty thoroughly said that -- maybe not all of us, but there's a group. Our discussion before was that Study 301 being negative makes it difficult to interpret Study 302 for all the statistical reasons considered before. But if you'll raise your hands, we can have discussion on this question now.

Dr. Emerson?

DR. EMERSON: Thank you. I'll just make three points in addition to what's there. The linear dose response, which much was made of that being one of Koch's postulates and things you want to do, none of this removed the fact that we did not have a linear dose response in 301 with no explanation of why it was there.

I'll note that I was very disturbed by some of the FDA's interpretation of 301 by starting out with the assumption that the treatment works, and now trying to assay why do we get no results in 301. Usually we start off saying the treatment doesn't work and are these compatible with it. And I spoke to this earlier about if you assume the
treatment doesn't work, then it's not that rare to have some strong results on one of the trials and just completely nothing results. And that's happened to me many times in my life when I've monitored trials of the same.

Then lastly, I was very, very, very disturbed by some of the analyses that were considered. I was glad to hear Dr. Dunn soften what they were doing and try to make clear. But I will just state that some 20 years ago I was involved as an expert witness in a scientific misconduct trial of, as it turns out, an Alzheimer's disease researcher who was removing beta that she didn't like and just seeing what happens, and that's just never acceptable to do.

So for the most part, the sensitivity analyses were sometimes just completely unnecessary. They were just reproducing the statistics we already had. I'd like to say that if you give me a study with a thousand subjects, I view that as a thousand subjects and I'm missing data on 7 billion others. And if you impute the
data on the 7 billion others, well, that's what we already do with statistics, and that's what it answers.

Then some of the other times, the missing data -- I believe it was Dr. Alexander who said earlier. But somebody said that the missing data analyses were not very comprehensive to the possibility of missing not at random, so I was bothered with that. So I'll just leave it at that.

DR. FOUNTAIN: Okay. Thank you.

Next is Dr. Gold.

DR. GOLD: Just a quick comment. I think I previously mentioned what I was struggling with is the notion that it was almost passively accepted that 302 represented truth and that 301 did not, and it's a lot of effort trying to discredit or to minimize the 301 data, so outlier analysis and rapid progressors.

But all those things are generally taken into account in the sample size estimates for the study, so I just didn't understand why there seemed to be this kind of unilateral effort to discredit
one study. It would have been interesting to take the opposite position to say 301 represents truth and what in 302 could have accounted for a false positive signal, just to kind of have either the falsifiable or counterfactual debate. So I think that's part of the issue in terms of how 301 influences 302.

The other part is, if you think about -- and I'm going back to some of the data that was presented earlier. Again, post-Amendment 4, the actual number of subjects that are impacted by that amendment in terms of dose escalation in the high-dose ApoE4 is miniscule. It's a really, really small number of subjects, and it's difficult for me to understand how big of an effect those subjects had in 302 to make the results as numerically positive as they are.

So I think it goes back to that first question. For me, it's difficult to divorce an understanding of 302 without thinking -- and it's kind of a Bayesian thing, prior information and prior knowledge. So I think it colored my
understanding or at least my level of comfort in the efforts to try to dismantle 301 and the lack of efficacy there.

    Again, this is a hugely important decision. Many of us came into industry because we dealt with Alzheimer's disease patients either personally or professionally. So I just want to unequivocally state that there is no lack of empathy and understanding of the misery and pain that the disease causes, but I think this is a hugely important decision that has and can have repercussions across clinical research enterprises and industry in terms of how do we interpret these kind of studies and what is the standard of evidence.

    So for me -- and I'll stop after this -- I think it's important to be respectful of the fact that 301 was well designed, well conducted, and well executed. There's no evidence that it was somehow defective in any way, shape, or form, and it's hard to ignore that. Thank you.

    DR. FOUNTAIN: Thank you.
Dr. Alexander?

DR. ALEXANDER: Thank you. I took my hand down. Thank you very much.

DR. FOUNTAIN: Okay. Dr. Duda?

DR. DUDA: Thank you. This is John Duda. I kind of agree with the prior speakers. I just want to say though, I think that it is noteworthy, the collaboration that developed between the FDA and the sponsor. I think obviously the sponsor was in a tough position. There were some decisions that were made that ended up probably not being beneficial to them. They had obviously put in a lot of resources into this compound, as has the field as a whole, and trying to find a way out of this unfortunate situation I think was laudable. I think more collaboration between the sponsors and the FDA is something that I'd like to see in future.

However, I think that perhaps in the future -- I don't think you would have gotten -- maybe you would have gotten people disagreeing with you that 301 was negative, but
instead of taking the approach of trying to explain that away, I guess a better approach might have been just to say, "Okay. Can we agree that 302 is positive?" If you had just gone down that route, we might not be where we are today.

But I think, all in all, the main -- I think several of us have said it already. Dr. Massie's criticisms just were never addressed in the clinical overview, and there seemed to be a disconnect between different aspects of the FDA reporting that are very difficult for us to draw conclusions from. So in light of that, I think it makes it much more difficult to get where the FDA maybe thought we would go today. Thank you.

DR. FOUNTAIN: Okay. And the last comment from Dr. Thambisetty.

DR. THAMBISETTY: Thank you, Dr. Fountain.

I think both 301 and 302 were well-designed phase 3 clinical trials and they provided discordant results. I don't think the post hoc exploratory analyses presented provide justification for discounting or overriding 301 and
considering 302 independently. Thank you.

DR. FOUNTAIN: Okay. Thank you.

Let's move to issue 8, which is a vote, question 8.

DR. DUNN: Can I just ask some of the folks who were commenting about how they feel about what we thought was clear on page 226? There's only so many pages we can write of the history of this. It's a short sentence, but I'm just kind of curious.

DR. ALEXANDER: Can you project it? This is Caleb Alexander. Would it be possible to project it? I don't know that I can find the materials easily.

DR. DUNN: Well, I could just read it.

"Upon initial review, the one positive study, Study 302, and the one negative study, 301, were given equal weight and consideration." And I suspect if you ask the applicant to weigh in, I think they will relate to you probably the degree to which 301 was given credence for a very long time, and it was quite clear that either study
could represent in the abstract truth.

   So I'm just curious about the comments because we wouldn't want to have conveyed that, and I'm wondering if that was missed or if it wasn't understood in the way that we intended it. That's kind of what I'm getting at. And I wouldn't mind asking the applicant actually to weigh in on that aspect because I don't think there was any sense of the people that were working on this that it was entered into with a belief in 302 a priori and a desire to throw 301 away. I remember taking great pains to make sure that wasn't the case.

   Maybe I can ask the applicant to weigh in on that and also if people could just clarify if we didn't communicate well our stance there.

   DR. HAEBERLEIN: Yes, thank you. That was absolutely the case through our investigations, that we treated both studies equally, and the resulting output of those investigations are indeed that Study 302 is robust and that Study 301 is a negative study. So that's not lending different weight to truth, but that those outcomes are
different. The nature of our investigations were to understand why Study 301 was a negative study.

DR. ALEXANDER: Dr. Dunn, if you review the briefing materials -- I'm trying to pull up selective pieces of them and -- and this is Caleb Alexander -- I can't do so quickly. But the framing of the briefing materials were very much -- at least I interpreted them as very much emphasizing an interest in identifying whether or not 301 could still provide sufficient evidence for 302 as a stand-alone pivotal study.

And the conclusion that was stated by the FDA used the words that the applicant has provided, "substantial evidence of effectiveness," and referred to 302 as a robust and exceptionally persuasive study. And I believe what you've heard today, as well as what's been communicated through the vote, is that -- I don't want to presumably speak on behalf of the entire committee, but certainly I do not feel that the evidence has been presented to support that view from the FDA.

So throughout the briefing materials in
many, many places, the emphasis is not on using 302
to understand why 301 was negative and raising the
question that perhaps 302 is really a negative
study, too. It's all framed in one direction,
which is using 301 to support 302. Thank you.

DR. PERLMUTTER: This is Joel Perlmutter.
Just to make a comment about impression of how the
data was presented to us is to just go to the first
discussion point. The first discussion point
seemed very biased in the sense that, okay, now
consider 302 and ignore everything in 301. That
just seems that we were being pushed in one
direction or there was a bias in that one
direction. So that really sums up how I perceived
the presentations.

DR. EMERSON: This is Scott Emerson. If you
thought that I was being critical, you're
absolutely correct. On page 226, one of the lines
that I felt was bad was you start off in saying,
"if it's effective," then it follows that that's
reflective of the two effects and there are
patients in Study 301 who, based on certain
characteristics, should show response.

Okay. The flip side is -- and I, again,
didn't have time earlier, but I was going to ask
for the analysis in which you added into Study 302
the patients who weren't represented that were
rapid progressors perhaps owing to the drug itself,
and you never did that analysis. So you were not
at all symmetric and you certainly were not
starting off with saying could these results be
explained by a null effect in which case you'd say,
yeah; nothing was going on in 301 -- that's the
truth -- and in 302, why did we get aberrant
results?

So the truth is probably somewhere in
between about the way to do it, but there was just
no question that all of this was just terrifically
one-sided. And again, I'm highly critical of the
fact that the FDA presentation today was so heavily
weighted to just giving the same conclusions that
the sponsor did, and that there was not
presentation by the statistician who'd done a
careful analysis and made many points that I was
very glad to see that the committee read.

DR. FOUNTAIN: I guess those points were clear. I guess in the briefing document the point was that they were considered individual, and one's positive and one's negative, and if it's positive, move forward.

Dr. Dunn, do you want us to vote on question number 8?

DR. DUNN: No, that's fine. I'm sorry. I didn't mean to interrupt too much there. I just wanted to make sure that we were communicating clearly as we need to. Thank you.

DR. THAMBISSETTY: Dr. Fountain, may I make a very quick point?

DR. FOUNTAIN: Sure, briefly.

DR. THAMBISSETTY: Very good. I just wanted to note that the discordant ways in which we have perceived this question I think is also very aptly summarized in the discordance between the FDA's clinical reviewer and the FDA's statistical reviewer. I think to paraphrase Dr. Tristian Massie, if you have two, and you take the best and
pretend like it's the only one, your estimate is likely biased. But I think that discordance is captured in the way the FDA's clinical review and statistical review differ as well. Thank you.

DR. FOUNTAIN: To summarize our discussion for this, all along we've said there's been no presumption 301 was positive; it's clearly negative. The general idea is that 302 is difficult to consider positive in light of 301 and that 103 had some evidence of pharmacodynamic effect as we generally said, but that's not necessarily supportive. As a parenthetical point, that the difference between the statistical analysis in Appendix 2 and the clinical reviewers is difficult for us to address.

So maybe we could move to point 8, the vote. In light of the understanding provided by the exploratory analysis of Studies 301 and Study 302, along with the results of Study 103 and evidence of a pharmacodynamic effect in Alzheimer's disease pathophysiology, is it reasonable to consider Study 302 has primary evidence of effectiveness of
aducanumab for the treatment of Alzheimer's
disease? Yes, no, or uncertain.

   We can discuss the nature of the question,
although I would say our last discussion was pretty
thorough.

Dr. Emerson, your hand is up. Do you have a
question about the wording of this one or is that
something else?

(No response.)

DR. FOUNTAIN: Okay. Thank you.

So now I think we can move to the vote.

DR. BONNER: We will now move voting numbers
to the voting breakout room to vote only. There
will be no discussions in the voting breakout room.

For the record, LaToya Bonner.

(Voting.)

DR. BONNER: LaToya Bonner. For the record,
the vote is now closed. We are tallying the
results. Once the vote results are displayed, I
will read the vote results into the record.

(Pause.)

DR. BONNER: LaToya Bonner, DFO. For vote
question 8, we have zero yeses, 10 nos, and
1 uncertain.

DR. FOUNTAIN: Thank you. We will now go
down the list and have everyone who voted state
their name and vote into the record. You may also
provide justification of your vote if you wish to.
We'll start again with Dr. Kesselheim.

DR. KESSELHEIM: Hi. Thank you. This is
Aaron Kesselheim. I voted no. First of all, I
also wanted to echo what others have said, to thank
the FDA, and the sponsor, and Dr. Massie in
particular, for their thorough reviews of the
material and very helpful presentations.

    I voted no for reasons that were discussed
in the prior conversation that I also discussed
earlier in these remarks today, so I'm not sure I'm
going to go over all of it again. Dr. Dunn pointed
out in his comments at the beginning of the day
that the evidence presented today provides
suggestive evidence of positive effectiveness that
the drug may be clinically active or that it's
possible that the results are persuasive.
I think all of those things are true. I don't think that the evidence in Study 302 provides substantial evidence of efficacy of effectiveness of this drug and the way that 301 was sliced and diced to support that further justifies that. So to the extent that this question is asking about the substantial evidence of efficacy standard, I don't think that meets the standard.

DR. FOUNTAIN: Thank you.

I'm next, Nathan Fountain. I voted uncertain because I do believe that 302 is positive and that 103 provides some additional evidence and there's some evidence in the markers. But of course 301 was clearly negative, and it's hard to say 302 could provide primary evidence, but it can't provide all the evidence or substantial evidence in my mind because of 301 and all the issues we discussed.

Dr. Duda?

DR. DUDA: This is John Duda. I voted no I think for all the reasons we've discussed and still the remaining questions I have regarding
Dr. Massie's analysis that I think is still not
completely addressed. Thank you.

DR. FOUNTAIN: Thank you.

Dr. Hoffmann?

DR. HOFFMANN: Richard Hoffmann. I voted no
also for many of the reasons that were noted. I
really don't think looking at Study 301 you can
transform that into a positive study using a
post hoc analysis, so I agree with the other
committee members. Thank you all very much, and I
also would like to thank the FDA and the sponsor
for all their efforts.

DR. FOUNTAIN: Thank you.

Dr. Kryscio?

DR. KRYSCIO: Yes. It's Richard Kryscio. I
voted no for the reasons already specified, and I
would like to as well join the chorus of thanking
both the Biogen company as well as the FDA for
great presentations and easy to read.

DR. FOUNTAIN: Thank you.

Dr. Perlmutter?

DR. PERLMUTTER: Yes. This is Joel
Perlmutter, and I voted no for all the reasons we discussed. But I specifically want to thank the sponsor for moving forward and implementing biomarker imaging to demonstrate target engagement. I think the problem is, over the years since they began it, it's not clear if that's in fact the right target. Thank you.

    DR. FOUNTAIN: Thank you.

Dr. Alexander?

    DR. ALEXANDER: This is Caleb Alexander. I voted no for all the reasons that I've previously specified, and thank you again to everyone involved in making today possible.

    DR. FOUNTAIN: Thank you.

Dr. Emerson?

    DR. EMERSON: I voted no and the reason has been stated. I'm going to answer a question that wasn't asked but often is.

What additional study would I want to see? I personally think that a randomized withdrawal of just the planned dose, and I'm uncertain of how long to treat them before you do the withdrawal.
But certainly one of the speakers in the public hearing remarked that they felt that they could tell quickly that they were not having the effect. Of course, I never know how true that is, but if that's true, a randomized withdrawal design wouldn't be as big a burden as would be some of the others and recognizing that in support, it should be done. I personally hope that this treatment pans out.

DR. FOUNTAIN: Thank you.

Dr. Thambisetty?

DR. THAMBISETTY: I voted no as well for all of the reasons discussed throughout the day, and I'd also like to take the opportunity to thank both the applicant and the FDA for the privilege of reviewing this hugely important work. I'd also add a special note of thanks to Dr. Tristan Massie for a really thorough statistical analysis that was very, very useful. Thank you.

DR. FOUNTAIN: Thank you.

Dr. Onyike?

DR. ONYIKE: Yes. This is Chiadi Onyike. I
voted no. I think the record speaks adequately to
the reasons why. I would like to also place on
record my thanks to the sponsor. This is a
substantive, multi-effort. These things are not
easy to put together. It takes a lot of
commitment, and as we all know, this is a very big
unmet need.

As well, I'd say my thanks to the people who
participated in this study, as well as to the
families and advocates who've testified today; and
to the FDA, and in particular to Dr. Tristan
Massie for his work; and to you, Dr. Fountain, for
shepherding us through the meeting today. Thank
you.

DR. FOUNTAIN: Thank you.

Dr. Jones?

DR. JONES: Yes. This is Dawndra Jones, and
I voted no. I think it's really hard to ignore
some of the things that we have identified through
Study 301 as well as many of the things we have
talked about today. But I, too, want to thank the
FDA and the applicant because this work is
critical, and it's critical and much needed for those patients and families that do suffer from Alzheimer's disease. So I am very hopeful that you will continue in this work so that we can definitely help the individuals that suffer from Alzheimer's. Thank you.

DR. FOUNTAIN: Thank you.

It looks like we have a consensus of opinion here about this question and mostly about all the questions. But before we adjourn, are there any last comments from the FDA?

DR. DUNN: No. Thank you for your time, very much appreciated

Adjournment

DR. FOUNTAIN: Thank you.

I'd just like to echo everyone else's appreciation to Biogen and the FDA, and all the FDA staff for putting together this production and all of you for working through with us. It's sort of like launching a space ship here to keep all of this straight. So I want to thank all of you, particularly the committee members who did such a
thorough job of reviewing the information, and also
the public speakers who went to all the effort and
trouble and distress, understandably speaking.

Thank you, everyone. We will now adjourn
the meeting. Thank you.

(Whereupon, at 5:06 p.m., the meeting was
adjourned.)