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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

1 **Dawndra Jones, DNP, RN, NEA-BC**

2 *(Consumer Representative)*

3 Chief Nursing Officer, VP Patient Care Services

4 University of Pittsburgh Medical Center

5 McKeesport Hospital

6 McKeesport, Pennsylvania

7
8 **Aaron S. Kesselheim, MD, JD, MPH**

9 Associate Professor of Medicine

10 Harvard Medical School

11 Division of Pharmacoepidemiology and

12 Pharmacoeconomics, Department of Medicine

13 Brigham and Women's Hospital

14 Boston, Massachusetts

15
16 **Richard J. Kryscio, PhD**

17 Professor, Statistics and Biostatistics

18 University of Kentucky

19 Sanders-Brown Center on Aging

20 Lexington, Kentucky

1 **Chiadi U. Onyike, MD, MHS**

2 Associate Professor of Psychiatry and
3 Behavioral Sciences

4 Division of Geriatric Psychiatry and
5 Neuropsychiatry

6 Department of Psychiatry and Behavioral Sciences
7 The Johns Hopkins University School of Medicine
8 Baltimore, Maryland

9
10 **Joel S. Perlmutter, MD**

11 Elliot Stein Family Professor of Neurology
12 Professor of Radiology, Neuroscience,
13 Physical Therapy & Occupational Therapy
14 Washington University School of Medicine
15 St. Louis, Missouri

1 **PERIPHERAL AND CENTRAL NERVOUS SYSTEM DRUGS**

2 **ADVISORY COMMITTEE MEMBER (Non-Voting)**

3 **Michael Gold, MS, MD**

4 *(Industry Representative)*

5 Vice-President

6 Neurosciences Development

7 AbbVie

8 North Chicago, Illinois

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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

1 **Richard P. Hoffmann, PharmD**

2 *(Patient Representative)*

3 Retired Pharmacist/Medical Writer

4 Patient Advocate/Parkinson's Foundation

5 Hernando, Florida

6
7 **Madhav Thambisetty, MD, PhD**

8 Senior Investigator and Chief

9 Clinical and Translational Neuroscience Section

10 Laboratory of Behavioral Neuroscience

11 National Institute on Aging

12 National Institutes of Health

13 Adjunct Professor of Neurology

14 Johns Hopkins University School of Medicine

15 Baltimore, Maryland

1 **FDA PARTICIPANTS (Non-Voting)**

2 **Eric Bastings, MD**

3 Acting Director, Division of Neurology I

4 Deputy Director, Office of Neuroscience (ON)

5 Office of New Drugs (OND), CDER, FDA

6
7 **Teresa Buracchio, MD**

8 Deputy Director

9 Division of Neurology I

10 ON, OND, CDER, FDA

11
12 **Billy Dunn, MD**

13 Director

14 Office of Neuroscience (ON)

15 OND, CDER, FDA

16
17 **Sally Jo Yasuda, PharmD**

18 Safety Team Leader

19 Division of Neurology I

20 ON, OND, CDER, FDA

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P R O C E E D I N G S

(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

1 introduce yourself by stating your name and
2 affiliation, and "I confirm."

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

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

10 DR. BONNER: Next is Dr. Fountain.

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

15 DR. BONNER: Next is Dr. Jones.

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

20 DR. BONNER: Thank you.

21 For the record, Dr. Gold, please introduce
22 yourself and your affiliation.

1 DR. GOLD: Hi. This is Dr. Michael Gold. I
2 am vice president and head of neurosciences
3 development at AbbVie. I'm a neurologist, and I'm
4 the nonvoting industry representative, and I
5 confirm.

6 DR. BONNER: Thank you, sir.

7 Dr. Kesselheim?

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

14 DR. BONNER: Thank you, sir.

15 Dr. Kryscio?

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

20 DR. BONNER: Next is Dr. Onyike.

21 DR. ONYIKE: Good morning. I'm Chiadi
22 Onyike. I'm a neuropsychiatrist and a psychiatric

1 epidemiologist, and an associate professor of
2 psychiatry and behavioral sciences at the Johns
3 Hopkins University. I confirm.

4 DR. BONNER: Thank you, sir.

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

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

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

17 DR. BONNER: Thank you, sir.

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

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

1 confirm.

2 DR. BONNER: Next is Dr. Hoffmann.

3 DR. HOFFMANN: Good morning. I'm Richard
4 Hoffman, the patient representative for this
5 meeting. I'm a retired pharmacist and medical
6 writer, and also the care partner for my wife who
7 14 years ago was diagnosed with Parkinson's
8 disease, which is the second most common
9 neurodegenerative disease next to Alzheimer's.

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

17 DR. BONNER: Thank you, sir.

18 Dr. Thambisetty?

19 DR. THAMBISETTY: Good morning, everyone.
20 Madhav Thambisetty. I'm a neurologist, a senior
21 investigator, and chief of the Clinical and
22 Translational Neuroscience Section at the National

1 Institute on Aging. I'm also an adjunct professor
2 of neurology at the Johns Hopkins University School
3 of Medicine.

4 DR. BONNER: Thank you, sir.

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

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

11 DR. BONNER: Dr. Bastings?

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

16 DR. BONNER: Thank you.

17 Next we have Dr. Buracchio.

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

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

1 ahead.

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

4 DR. BONNER: I will now turn the meeting
5 back over to the chair.

6 Dr. Fountain?

7 DR. FOUNTAIN: For topics such as those
8 being discussed in this meeting, there are often a
9 variety of opinions, some of which are quite
10 strongly held. Our goal is that this meeting will
11 be a fair and open forum for discussion of these
12 issues and that individuals can express their views
13 without interruption. Thus, as a gentle reminder,
14 individuals will be allowed to speak in the record
15 only if recognized by me, the chairperson. We look
16 forward to a productive meeting.

17 In the spirit of the Federal Advisory
18 Committee Act and the Government in the Sunshine
19 Act, we ask that the advisory committee members
20 take care that their conversations about the topic
21 at hand take place in the open form of the meeting.
22 We are aware that members of the media are anxious

1 to speak with the FDA about these proceedings,
2 however, the FDA will refrain from discussing the
3 details of this meeting with the media until its
4 conclusion. Also, the committee is reminded to
5 please refrain from discussing the meeting topic
6 during breaks or lunch. Thank you.

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

9 **Conflict of Interest Statement**

10 DR. BONNER: Thank you.

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

21 The following information on the status of
22 this committee's compliance with federal ethics and

1 conflict of interest laws, covered by but not
2 limited to those found at 18 U.S.C. Section 208, is
3 being provided to participants in today's meeting
4 and to the public.

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

19 Related to the discussions of today's
20 meeting, members and temporary voting members of
21 this committee have been screened for potential
22 financial conflicts of interests of their own as

1 well as those imputed to them, including those of
2 their spouses or minor children and, for purposes
3 of 18 U.S.C. Section 208, their employers. These
4 interests may include investments; consulting;
5 expert witness testimony; contracts, grants,
6 CRADAs; teaching, speaking, writing; patents and
7 royalties; and primary employment.

8 Today's agenda involves the discussion of
9 biologics application 761178, for aducanumab
10 solution for intravenous infusion, submitted by
11 Biogen Incorporated, for the treatment of
12 Alzheimer's disease. This is a particular matters
13 meeting during which specific matters related to
14 Biogen's BLA will be discussed.

15 Based on the agenda for today's meeting and
16 all financial interests reported by the committee
17 members and temporary voting members, no conflict
18 of interest waivers have been issued in connection
19 with this meeting. To ensure transparency, we
20 encourage all standing committee members and
21 temporary voting members to disclose any public
22 statements that they have made concerning the

1 product at issue.

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

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

21 I will now turn the meeting back over to the
22 chair.

1 DR. FOUNTAIN: Thank you.

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

5 Dr. Dunn?

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

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

9 **FDA Introductory Remarks - Billy Dunn**

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

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

20 I want to especially thank the public
21 attendees for their commitment to developing safe
22 and effective treatments for Alzheimer's disease.

1 I particularly want to note and thank those who may
2 be affected by Alzheimer's disease who are joining
3 us today. For those of you who have requested an
4 opportunity to address the committee or who have
5 provided written comments for the committee, we
6 look forward to and are deeply appreciative of your
7 input. Your efforts to be here are invaluable and
8 tremendously appreciated. Thank you.

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

17 Although there are four unique drugs
18 approved and currently marketed for the treatment
19 of Alzheimer's disease, current treatments,
20 valuable though they are, do not target the
21 underlying pathology of Alzheimer's disease and
22 have only a modest reversible symptomatic effect of

1 limited duration. These drugs, approved from 1996
2 to 2003, have been unable to alter the relentless
3 progression of Alzheimer's disease.

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

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

20 Today, following my remarks, you will first
21 hear a summary presentation from the applicant
22 reviewing important aspects of the data presented

1 in support of aducanumab's approval. After that, I
2 will return to discuss the issues involved in
3 consideration of these data. The reason we are
4 here today is to gain your input into some of the
5 issues we have confronted during our review
6 process. Thank you for the substantial efforts you
7 have made in preparing for and attending this
8 meeting, and thank you for the important work you
9 will do today.

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

13 DR. FOUNTAIN: Thank you.

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

21 For this reason, FDA encourages all
22 participants, including the applicant's

1 non-employee presenters, to advise the committee of
2 any financial relationships that they may have with
3 the sponsor such as consulting fees, travel
4 expenses, honoraria, and interest in the sponsor,
5 including equity interests and those based upon the
6 outcome of the meeting.

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

14 We will now proceed with Biogen's
15 presentation.

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

19 DR. BONNER: Yes, we can hear you well.
20 Thank you.

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

1 Thank you.

2 **Applicant Presentation - Samantha Budd Haeberlein**

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

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

22 Alzheimer's is a truly terrible disease.

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

12 We have submitted a biologics license
13 application seeking approval of aducanumab to delay
14 clinical decline in patients with Alzheimer's
15 disease. The recommended dosage is 10-milligram
16 per kilogram intravenous infusion every 4 weeks
17 following a titration period. We are here today
18 because aducanumab, a molecule that targets the
19 underlying pathophysiology of Alzheimer's disease,
20 is the first such therapeutic to show a reduction
21 in clinical decline in patients with Alzheimer's
22 disease. However, this important first for the

1 disease is set against the backdrop of some unusual
2 circumstances.

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

16 Given these unusual circumstances, we sought
17 the advice of the FDA. This led to four
18 Type C meetings over 12 months. We began these
19 discussions from the premise that Studies 301 and
20 302 were equally informative. Through rigorous and
21 focused analyses, we determined that Study 302 is a
22 robust positive study and that Study 301 is

1 negative but does not detract from Study 302. And
2 on this basis the FDA advised that Biogen submit a
3 marketing application for the approval of
4 aducanumab.

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

13 Study 302 fulfills these criteria. It is a
14 multicenter trial that enrolled 1,638 patients in
15 13 countries. Study 302 has dose-dependent,
16 statistically significant and clinically meaningful
17 effects on multiple distinct endpoints of
18 Alzheimer's disease symptomatology. It is
19 profoundly consistent, having met the primary
20 endpoint with a p-value close to 0.01, met all
21 secondary endpoints, and has shown consistency
22 across patient subgroups.

1 Study 302 has also demonstrated effects on
2 multiple objective biomarkers of disease pathology.
3 The probability of such consistency being a false
4 positive is very small. After reviewing the data,
5 the FDA concluded that Study 302 is robust and
6 exceptionally persuasive. The FDA also agreed that
7 supportive evidence comes from Study 103. It was
8 an earlier study designed for proof of concept but
9 was nonetheless an adequate and well-controlled
10 study and demonstrated a positive outcome for the
11 high dose.

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

1 from the prerecorded presentations.

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

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

22 New innovations, including longitudinal

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

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

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

20 This is very different from other anti-A
21 beta antibodies such as solanezumab and
22 bapineuzumab, and contributes to the high

1 selectivity of aducanumab for toxic aggregated
2 forms of beta-amyloid, and it's low binding to
3 non-toxic monomers. Beta-amyloid generates
4 different forms along the aggregation pathway, from
5 monomers into oligomers, protofibrils, and
6 elongation of protofibrils into fibrils.
7 Aducanumab specifically binds to the aggregated
8 forms of beta-amyloid in this pathway.

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

16 I will now review the clinical studies
17 starting with Study 103. Study 103, although
18 designed primarily as a safety and tolerability
19 study, was an adequate and well-controlled study
20 which explicitly included prespecified clinical and
21 biomarker endpoints. Study 103 was a 12-month
22 staggered cohort, dose-ranging study in which

1 aducanumab demonstrated dose and time-dependent
2 reduction of the pharmacodynamic biomarker
3 beta-amyloid plaque as measured by PET. On the
4 left are selected beta-amyloid PET images from the
5 different dosing cohorts.

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

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

22 These results confirmed that aducanumab was

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

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

16 We used PET in our studies, although today,
17 CSF tests are also validated for this purpose. We
18 learned in Study 103 that reduction in beta-amyloid
19 pathology was detectable early and before changes
20 in the clinical endpoints, with clinical effects
21 being measurable at 12 months. The CDR sum of
22 boxes were shown to be sensitive to change and

1 thereby validated as an appropriate endpoint in
2 this patient population. We discussed and gained
3 FDA support for CDR sum of boxes as a single
4 primary endpoint through our special protocol
5 assessment.

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

16 Ten milligram per kilogram was selected as
17 the target dose for phase 3 based on being the most
18 efficacious on biomarker and clinical endpoints.
19 To mitigate ARIA, our phase 3 studies included
20 titration to target dose, a lower dose, and doses
21 were stratified, at least in the beginning, by
22 ApoE4 gene carrier status.

1 In these next slides I will review
2 Studies 302 and 301. In Study 302, aducanumab met
3 its primary endpoint, demonstrating a 22 percent
4 reduction in decline versus placebo on CDR sum of
5 boxes at week 78 and with a p-value of 0.0120.
6 Missing data is always a challenge, especially in
7 long trials in Alzheimer's disease.

8 Our analyses had an assumption of 30 percent
9 missing data in line with contemporary clinical
10 trials in this population. During the conduct of
11 the trial, we actually had only half of that degree
12 of patient dropout. Due to the early termination,
13 the administrative censoring takes us up to
14 45 percent missing data, which is 15 percent more
15 than planned at the design stage.

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

1 p-value of 0.03.

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

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

20 In addition to analyses to assess missing
21 data, we assessed if baseline factors influenced
22 the treatment effect in Study 302. In a large

1 global study with long enrollment, some fluctuation
2 in baseline factors can be expected. In the
3 analyses summarized here, we are assessing how the
4 baseline factors such as ApoE4, baseline disease
5 severity, and gender influence the overall
6 treatment effect.

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

15 The results are very consistent. Baseline
16 factors and their interactions only explained a
17 very small amount of variability in clinical
18 outcomes between treatment groups. Of note, in
19 these analyses the country by treatment interaction
20 was identified to be nominally significant,
21 indicating there were some differences in
22 countries. Therefore, on the next slide we

1 examined how the country effect influenced the
2 overall treatment effect.

3 We added the country by visit, country by
4 treatment, and country by treatment by visit
5 interactions to the primary analysis model.
6 Fitting these interactions resulted in a consistent
7 treatment effect of 0.40 and with a p-value of
8 0.0105.

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

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

22 Here are the U.S. only results for the

1 primary and three secondary outcomes. The
2 treatment effect on CDR sum of boxes is 0.55, a
3 32 percent reduction in decline compared to
4 placebo. Corresponding results on secondary
5 outcomes showed reductions of 28 percent and
6 29 percent on MMSE and ADAS-Cog13, with a
7 57 percent reduction in decline on activities of
8 daily living.

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

15 Turning our attention to the overall
16 prespecified study results, focusing here on the
17 results for the prespecified secondary endpoints,
18 in addition to the robust significance on the
19 primary endpoint of CDR sum of boxes, the high-dose
20 arm of Study 302 met all secondary endpoints
21 according to our prespecified multiple comparison
22 approach that was included as part of the special

1 protocol assessment agreement with the FDA.

2 The reductions in decline ranged from 18 to
3 40 percent versus placebo, with the high dose
4 reaching significance in every case. In each
5 endpoint, we see a greater reduction in the
6 high-dose group, demonstrating, as with the primary
7 endpoint, a dose-response relationship.

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

14 Principal components analyses conducted and
15 shared with the FDA showed that these four
16 endpoints measured different aspects of Alzheimer's
17 disease and have minimal overlap. Hence,
18 aducanumab reduced clinical decline across multiple
19 assessments, which cover broad aspects of cognition
20 and function. The internal consistency across the
21 four prespecified clinical endpoints is
22 exceptional. Based on the observed treatment

1 effect and correlations between the endpoints, the
2 probability that these are false positive results
3 is about 1 in 10,000.

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

13 In addition to effects on brain beta-amyloid
14 plaques, aducanumab showed significant
15 dose-dependent effects on biomarkers of downstream
16 Alzheimer's pathology. Here we see phosphorylated
17 tau, a biomarker of Alzheimer's specific pathology
18 measured in CSF. It shows that aducanumab provides
19 dose-dependent and nominally significant
20 reductions. Further, total tau, a biomarker of
21 neurodegeneration also measured in CSF, showed
22 similar reductions.

1 Our analyses, based on all patients, showed
2 significant correlations of these biomarkers with
3 clinical changes. Taken together, the various
4 imaging and fluid biomarker results are consistent
5 with a direct effect of aducanumab on lowering
6 brain beta-amyloid pathology with a subsequent
7 effect on reducing tau pathology and
8 neurodegeneration.

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

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

1 Study 302.

2 In addition, the effect on phosphorylated
3 tau in the CSF was 51 percent smaller in the
4 high-dose group in Study 301 than in Study 302 and
5 the cumulative dose in the CSF subgroup was
6 20 percent smaller than in Study 302. These data
7 provide an important insight, namely differences in
8 actual doses received by the patients in
9 Studies 301 and 302 contributed to the difference
10 in results.

11 In summary, the results of the two phase 3
12 trials were partially discordant. The results were
13 similar in the low-dose groups across clinical and
14 biomarker measures. On initial review of the data,
15 the FDA stated that a marketing application may be
16 considered based primarily on the results of
17 Study 302 as a single positive efficacy study. It
18 was stated that resources should be brought to bear
19 on achieving a maximum understanding of the
20 existing data, and in particular to investigate
21 whether the results of Study 301 may have a role in
22 supporting Study 302 or may be understood well

1 enough to not detract from Study 302; in other
2 words, to not represent evidence that the drug is
3 ineffective.

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

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

20 As noted in the briefing materials, after
21 these analyses, we and the agency concluded that
22 the results from Study 301 do not detract from the

1 persuasiveness of Study 302. It's important to
2 appreciate that "does not detract" is very
3 different from saying "we can't ignore." Based on
4 the totality of the evidence, demographics and
5 baseline disease characteristics were similar
6 between the studies and do not have a meaningful
7 impact on the outcome of the studies.

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

19 However, meaningful subgroups in Study 301
20 had results similar to 302, specifically in
21 patients who were randomized to groups with the
22 opportunity to receive 14 doses of 10 milligram per

1 kilogram, and there were no findings that
2 represented evidence that aducanumab is not
3 effective.

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

11 Patients who had the opportunity to receive
12 14 doses of 10 milligram per kilogram had similar
13 benefit in both studies. The three high-dose
14 groups who were randomized to have the opportunity
15 for the full doses of 10 milligram per kilogram
16 were ApoE4 non-carriers before and after
17 Protocol 4, and the ApoE4 carriers after Protocol
18 version 4 was implemented.

19 When combining the data across these groups,
20 the weighted mean in each study showed a 23 percent
21 reduction in clinical decline relative to the
22 corresponding placebo groups on the CDR sum of

1 boxes; that is the dose regimen for which we are
2 seeking approval was efficacious to a similar
3 extent in both studies. The discordance between
4 the studies arose from the subset of patients who
5 did not have access to full 10 milligram per
6 kilogram dosing.

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

19 Moving to look at a review of safety, as you
20 have heard from Dr. Smirnakis, the safety profile
21 of aducanumab is well characterized based on more
22 than 5,300 person-years of follow-up for aducanumab

1 treated patients. This table shows the most common
2 AEs that were also more frequent among aducanumab
3 treated patients with a target dose of 10 milligram
4 per kilogram. The most common AE among aducanumab
5 treated patients was an MRI finding ARIA-E. Other
6 common AEs were headache, brain microhemorrhage,
7 fall, superficial siderosis, and diarrhea, two of
8 these also being radiographically detected.

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

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

1 mild or moderate in severity.

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

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

16 In clinical practice, as in the aducanumab
17 clinical trials, ARIA risk mitigation will be
18 important and will include dose titration, the use
19 of MRI monitoring, particularly during the early
20 treatment period, and dose suspension as needed.
21 We recognize that if aducanumab is approved, ARIA
22 will be a novel MRI finding and clinical entity for

1 many clinicians and patients. Therefore, we are
2 committed to educating prescribers, radiologists,
3 patients, and their caregivers on the risk of ARIA
4 and its management.

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

13 In addition to reducing declines in memory
14 and cognition, aducanumab impacts many of the items
15 in the Activities of Daily Living scale. The
16 40 percent reduction in decline in the total score
17 represents approximately 7 months more time with
18 retained independence in the context of the
19 18-month trial period. Aducanumab also showed
20 dose-dependent reduction versus placebo in the
21 Neuropsychiatric Inventory score, which assesses
22 behavioral symptoms such as anxiety, agitation, and

1 aggression, and these symptoms are very troubling
2 for patients and their families. These benefits
3 were observed in patients with a limited baseline
4 severity and against a backdrop of minimal expected
5 disease progression over this time frame.

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

13 Across the three studies in patients with
14 Alzheimer's disease who had consistent exposure to
15 10 milligram per kilogram, aducanumab demonstrated
16 a reduction in clinical decline. This means that
17 patients who responded to aducanumab were able to
18 better function, resonate, and interact with others
19 than the patients who received placebo.

20 Given the totality of the evidence, we can
21 conclude that the benefit-risk profile for
22 aducanumab is favorable and potentially prolongs

1 patients' independence by several months, even a
2 few years, as demonstrated in our long-term study.
3 This matters for the patient, their loved ones, and
4 society. Considering the tremendous unmet need and
5 devastating nature of this disease on patients and
6 their families, we conclude that aducanumab is an
7 important new option for patients with Alzheimer's
8 disease.

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

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

1 bring this to patients and families.

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

6 **Clarifying Questions to Applicant**

7 DR. FOUNTAIN: Alright. We will now take
8 clarifying questions for Biogen. Please use the
9 raised-hand icon to indicate that you have a
10 question and remember to lower your hand by
11 clicking the raised-hand icon again after you've
12 asked a question.

13 When acknowledged, please remember to state
14 your name for the record before you speak and
15 direct your question to a specific presenter if you
16 can. If you wish for a specific slide to be
17 displayed, please let us know the slide number if
18 possible. Finally, it will be helpful to
19 acknowledge the end of your question with a thank
20 you and end of your follow-up question with, "That
21 is all for my question," so we can move on to the
22 next panel member.

1 We'll begin with a question from
2 Dr. Hoffmann.

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

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

18 We use PET, but there are additional
19 modalities available today, which will make that an
20 easier access in comparison to the use of PET
21 previously. Technologies such as CSF are already
22 validated, and we are excited that there is

1 potential for blood biomarkers to also be available
2 in the near future.

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

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

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

19 DR. HAEBERLEIN: The indication that we are
20 seeking is for the treatment of Alzheimer's
21 disease. The clinical trial population that we had
22 were of a disease stage of MCI due to AD or mild AD

1 for those patients with symptoms. Sorry. I was
2 focusing on your question in regards to
3 asymptomatic.

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

9 DR. HOFFMANN: Okay. Thank you very much.

10 DR. HAEBERLEIN: Thank you.

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

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

20 Can you clarify the extent to which the
21 collection of data, that is which study and what
22 data set, was prespecified, and if they were

1 prespecified, if evidence of the discordant results
2 are truly uncommon under the null hypothesis?

3 DR. HAEBERLEIN: Dr. Mallinckrodt, please?

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

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

19 There are other data sets that additionally
20 provide information such as the opportunity to
21 complete and the uncensored analysis. So the
22 results we are presenting today are results that

1 hit the bullseye after the target was painted not
2 before the target was painted. Thank you.

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

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

15 DR. EMERSON: In both studies.

16 DR. HAEBERLEIN: In both studies.

17 DR. EMERSON: Okay. So just doing a simple
18 Bonferroni correction, that p-value that you're
19 quoting at 0.012, I don't know how to correct for
20 the idea that you are looking at something
21 different than the futility analysis data set. I
22 don't know how to correct for a lot of the other

1 decisions that you might have considered. But
2 certainly I can correct for you looking for the
3 minimum of two p-values in which case -- well,
4 assuming that they're both independent, that 0.012
5 is not a true p-value. A true p-value would be
6 closer to 0.0233 just adjusting for that aspect, no
7 other multiplicity.

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

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

22 Do you have an alternative calculation to

1 this idea of this 40 percent chance, this idea that
2 it's this discordant, given the way that you
3 sampled which results you were going to present to
4 us, that this p-value would be wrong?

5 DR. HAEBERLEIN: Dr. Mallinckrodt, please?

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

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

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

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

21 DR. EMERSON: -- yes. What I need to know
22 is --

1 (Crosstalk.)

2 DR. MALLINCKRODT: So we don't have a
3 multiplicity issue across data sets; that's an
4 important aspect. When we look at the results of
5 Studies 301 and 302, it is almost certain that the
6 difference between the study results are not due to
7 chance alone. We've anchored probabilities for
8 Study 302 with its positivity across all endpoints.

9 We understand that the differences between
10 301 and 302 are not due to chance alone. We have
11 identified rapid progressors and dosing as causal
12 reasons for the difference.

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

1 calculating the random chance of randomization
2 imbalances.

3 So I disagree with your statement, and my
4 question again is, conditional upon performing two
5 studies and coming back to the FDA when a post hoc
6 analysis has demonstrated a nominal p-value of
7 0.012, which after you adjust for the multiplicity,
8 that you didn't prespecify which of those two
9 independent studies would do it -- would be point
10 .0233 -- but now again, that selection pressure on
11 only coming to us when you've got some promising
12 results, under the null hypothesis, how often would
13 we expect to see -- so the true null -- that the
14 other study would have a result as discordant as
15 we've seen here?

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

22 DR. MALLINCKRODT: We do not have that

1 particular p-value. The p-values that we have are
2 based on the prespecified analysis plan for
3 Study 302, showing statistical significance on all
4 the endpoints.

5 DR. EMERSON: Okay. But that prespecified
6 plan was violated because you're only presenting
7 302, and that was not prespecified. And I will
8 also note -- and I'll stop questioning after this.
9 But I will come back later to this issue of your
10 looking at these different results and what's
11 discordant and trying to throw out
12 post-randomization data. So I'll stop there for
13 now. Thank you.

14 DR. FOUNTAIN: Okay. Thank you.

15 Now we'll turn to Dr. Kesselheim.

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

22 DR. HAEBERLEIN: Thank you. Study 104 was a

1 small study conducted in Japan, as it is important
2 in clinical development to include Japan in
3 late-stage clinical trials. So that was a safety
4 and tolerability study examining a single dose and
5 multiple dose in a very small number of
6 individuals. You'll see that there was 21 in
7 total. Slide up, please. So that information,
8 which is included in our overall BNA [ph], is not
9 part of the conversation in regards to substantial
10 evidence of effectiveness.

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

22 DR. FOUNTAIN: Thank you. If that answers

1 your question, we'll move to Dr. Onyike.

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

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

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

22 DR. HAEBERLEIN: Thank you very much for

1 your question, for the multiple parts. First, I'll
2 address the second two parts of your question
3 there, so the number of individuals who were
4 rapidly progressing in the placebo groups. If we
5 can have the slide of numbers of rapid progressors.

6 You correctly point out -- slide up,
7 please -- that the presence of rapidly progressing
8 individuals is not only in treatment arms but are
9 also found in the placebo arms of both studies.
10 And here you can see that there was an equal
11 distribution of 4 patients who had a greater than
12 8-point decline on CDR sum of boxes by week 78, so
13 really a very extreme progression of those
14 individuals. Slide down, please.

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

1 particular on the primary endpoint.

2 You can see here in each of the arms of both
3 studies, the dotted line represents the placebo
4 decline, which in both studies was within the
5 anticipated placebo decline. I'll ask
6 Dr. Mallinckrodt to speak a bit more about that in
7 a second, but first just to emphasize that those
8 individuals who were rapidly progressing, you can
9 see their trajectories here were
10 really quite dramatically departing from the
11 expected or from the placebo decline. This is on a
12 0 to 18-point CDR sum of boxes, and 18 points on
13 the CDR sum of boxes equates to somebody who is
14 bed-bound, incontinent, and completely dependent.
15 So these are really a malignant form of Alzheimer's
16 disease. Thank you. Slide down, please.

17 In regards to your question on the
18 proportion of individuals who were mild cognitive
19 impairment due to Alzheimer's disease in each of
20 the studies, we can bring that up here. We had a
21 target for enrollment such that we would have
22 approximately 80 percent individuals who were MCI

1 due to AD at baseline. You can see to the lower
2 end of the table here, clinical stage at baseline.
3 In Study 301, overall there were 80.4 percent with
4 MCI due to AD at baseline. In Study 302, that was
5 81.6 percent and quite balanced across arms.

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

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

20 DR. ONYIKE: Before you invite him, may I
21 ask how these distributions in the placebo group,
22 MCI versus AD, look at study end?

1 DR. HAEBERLEIN: At the conclusion of the
2 study, I'm not sure that I have that figure
3 available for you. If that's important, maybe
4 that's something I can ask my team to find and
5 bring up at a later point, if that would be
6 important for you.

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

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

15 DR. ONYIKE: Yes. Thank you.

16 DR. HAEBERLEIN: Thank you.

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

21 The slide we're showing now depicts how
22 placebo response or placebo decline changed during

1 the course of this study, and this is done by
2 cohorts of every 200 patients, approximately
3 one-third of which were on placebo. In both
4 Studies 301 and 302, we see fluctuations over time.
5 The line in the center of the box represents the
6 median, the diamond represents the mean. And you
7 can see in the numbers at the bottom of the slide
8 how these placebo means fluctuated across the
9 various cohorts over time, but no systematic trend
10 in either study.

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

19 Placebo decline at week 78 varied by
20 endpoint. We had greater decline in Study 302 on
21 the CDR and the ADL, but less decline in 302 on the
22 MMSE and similar decline on ADAS-Cog13. Perhaps

1 most importantly, the treatment effect for the low
2 dose was consistent between Studies 301 and 302,
3 suggesting differences between studies and placebo
4 decline was unlikely to have had a major influence
5 on the high-dose group.

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

13 DR. ONYIKE: Thank you.

14 DR. FOUNTAIN: Thank you.

15 Next, we'll move to Dr. Thambisetty.

16 DR. THAMBISETTY: Thank you, Dr. Fountain.
17 Madhav Thambisetty. I have a two-part question.
18 The first pertains to Study 103. Unlike
19 Studies 301 and 302, the data and results from
20 Study 103 have been subjected to independent peer
21 review and were actually published in 2016 in the
22 Nature paper by Jack Sevigny and colleagues.

1 In Study 103, in addition to the CDR sum of
2 box scores and MMSE, there were three other
3 co-equal exploratory endpoints, so all of these
4 endpoints were stated to be exploratory. In
5 addition to the CDR sum of boxes and MMSE, there
6 were also assessments made on the NTB, which has
7 9 validated components; the Free and Cued Selective
8 Reminding Test; as well as the Cognitive Drug
9 Research computerized test battery.

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

18 The chances of type 1 error in these
19 unadjusted comparisons are extremely high to say
20 the least. Do you have a sense for what the risk
21 of type 1 error would be in these exploratory
22 analyses that were previously reported? That's my

1 first question, and if Dr. Fountain permits me to
2 come back, I'll wait for the answer and then ask
3 another question. Thank you.

4 DR. HAEBERLEIN: Dr. Mallinckrodt, please.

5 DR. MALLINCKRODT: Craig Mallinckrodt,
6 Biogen. We do not have the specific p-values
7 encompassing a global family of tests across the
8 Study 103 endpoints. However, we do note, as
9 you've seen in the sensitivity analyses, the
10 treatment effect estimates for the CDR and MMSE,
11 along with the A-beta results, the biomarker
12 results, are consistent between Studies 103 and
13 302, and it is that consistency that forms the
14 primary basis for our utilization of Study 103 in
15 support of the positivity of Study 302. Thank you.

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

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

21 DR. FOUNTAIN: Okay.

22 DR. ONYIKE: The instance of ARIA-E is

1 35 percent in the treatment group compared to
2 2.7 percent in the placebo group. I'd like to know
3 how the diagnosis of ARIA is communicated to the
4 patient and their caregivers. Are they told that
5 they have brain swelling or microbleeds in the
6 brain that require them to come in for a previously
7 unscheduled MRI scan? And if that is the case, are
8 they also told that they would have to keep coming
9 back for an MRI scan until these abnormalities
10 improve, and until such abnormalities improve, that
11 their dose of medication or placebo would have to
12 be held?

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

18 DR. HAEBERLEIN: Thank you.

19 Dr. Chalkias, please.

20 DR. CHALKIAS: Spyros Chalkias, Biogen.
21 Thank you for the question. The patients are aware
22 of the MRI results, and then they're asked to come

1 back for a follow-up MRI that's done every 4 weeks
2 to document resolution of ARIA. Thank you.

3 DR. FOUNTAIN: Thank you.

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

8 Next, we'll turn to Dr. Alexander.

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

15 I think, Dr. Mallinckrodt, you recently
16 said -- you used the word "causal" in referring to
17 rapid progressors and dosing differences as
18 explaining the failure of 301, and I don't see it.
19 With rapid progressors, we're talking about a
20 difference of 4 or 5 people in a group containing
21 500 or more, and this theory of rapid progressors
22 was introduced I believe only post hoc. And other

1 methods of examining outliers, other outlier
2 analyses, that may be more suitable, such as robust
3 regression or trimmed means, also failed to
4 replicate the findings of 302 in looking at 301.

5 It reminds me a little bit of a separate
6 committee, where there was a subset of individuals
7 that appeared to be responding particularly well,
8 and I think a member of the committee used the term
9 "super responders." So I understand the appeal of
10 trying to identify and explain away the null
11 findings, but I don't think that the evidence is
12 there. I'd say the same for dosing differences,
13 and I think we'll have a chance to get into that
14 further later today.

15 I want to turn then to placebo response, and
16 while you provided some helpful information, you
17 didn't include, I think, the graphical illustration
18 that I think is most troublesome to me, which I'm
19 sure you're familiar with, which was included in
20 the biostatistical review by the FDA. I don't know
21 if that can be presented or if you have an
22 identical depiction of the data, but essentially

1 that stratifies and looks at ApoE4 positive
2 pre-Protocol Amendment 4 versus post-Protocol
3 Amendment 4.

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

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

18 DR. HAEBERLEIN: Thank you for that
19 question, and Dr. Mallinckrodt will comment on that
20 particular analysis, the specific question you had
21 there. I just want to appreciate
22 your thoughts on why so much work was brought to

1 bear on trying to understand the partially
2 discordant results of Study 301.

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

16 So it's difficult to therefore --

17 DR. ALEXANDER: If I could interrupt one
18 minute. My question was about the placebo, the
19 separation of the placebo curves. But I think if
20 you're bringing up the consistency across multiple
21 endpoints, it's also worth calling out another
22 point raised by the FDA biostatistical review, and

1 correct me if I'm wrong here. But I believe that
2 they indicated that because the low-dose primary
3 endpoint was not met, technically the secondary
4 high-dose endpoints can't be formally evaluated.
5 And in fact the correlation between the primary and
6 secondary endpoints was moderate with correlation
7 coefficients of 0.4 to 0.64, regardless of what
8 principal components analysis may have suggested.

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

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

22 DR. ALEXANDER: Okay. I'm sorry to

1 interrupt, but I know that I --

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

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

16 DR. HAEBERLEIN: Thank you.

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

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

21 Dr. Mallinckrodt, please.

22 DR. MALLINCKRODT: Craig Mallinckrodt,

1 Biogen. We're going to be looking at results by
2 ApoE carrier status pre- and post-PV4. Let's first
3 focus on the placebo decline column. Pre-PV4, the
4 carriers were 1.65, and post-PV4, carriers were
5 1.92, both well within the anticipated placebo
6 response for the entire study cohort.

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

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

1 slightly difference in the scale.

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

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

22 When we look more broadly across all the

1 data, we see no systematic trends, but that doesn't
2 mean there isn't some cohort --

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

5 DR. MALLINCKRODT: -- along the way --

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

8 DR. MALLINCKRODT: Thank you.

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

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

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

18 **FDA Presentation - Billy Dunn**

19 DR. DUNN: Thank you, Dr. Fountain.

20 I'm going to spend the next few minutes
21 discussing some of the issues involved in the
22 consideration of the aducanumab marketing

1 application and why the evidence supporting its
2 approval appear strong.

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

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

21 There has not been an approval of a novel
22 medication for the treatment of Alzheimer's disease

1 since 2003. Aducanumab targets amyloid-beta, the
2 fundamental pathological hallmark of the disease.
3 Although there have been previous failures of other
4 drugs that have been intended to target
5 amyloid-beta in some fashion, there are features of
6 aducanumab's pharmacologic profile and of the
7 design of its clinical development program that are
8 novel and distinguish it from prior efforts with
9 these other agents.

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

20 Subsequent examination of individual study
21 results, that included additional data that had
22 accrued during the time that the futility analysis

1 was being conducted, revealed findings differed
2 from the results of the prespecified futility
3 analysis, most notably including apparently
4 positive results in Study 302.

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

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

22 The notably long duration and thorough

1 nature of presubmission review affords a
2 particularly complete consideration by the FDA of
3 the evidence of effectiveness to be discussed at
4 this meeting. The evidence presented by the
5 applicant in the application in support of
6 aducanumab's effectiveness is essentially unchanged
7 from that which has been considered throughout the
8 presubmission phase.

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

16 As you've heard from the applicant and seen
17 in the background materials, after declaring
18 futility, according to the sponsors prespecified
19 utility analysis, the sponsor moved to explore the
20 individual study results, which included additional
21 data that had accrued while the futility analysis
22 was being conducted and recognized that the results

1 were surprising and inconsistent with what was
2 expected from the futility analysis.

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

15 Upon reviewing the data, it was immediately
16 apparent that the results of the primary endpoint
17 for the high-dose groups differed dramatically
18 between studies. Although this finding naturally
19 received a great deal of attention at the meeting,
20 one of the important things that we immediately
21 noted was a remarkable degree of concordance
22 between results in the low-dose groups in both

1 studies. In addition, the positive results in the
2 high-dose group --

3 MALE VOICE: Hi. I'm sorry. I stepped
4 away. Please.

5 leave me a message and I'll call you back as soon
6 as I can. Thanks. Bye.

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

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

12 DR. DUNN: Alright. I'll continue.

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

18 In addition, the positive results in the
19 high-dose group of Study 302 was strongly supported
20 by the effects on the secondary outcomes in the
21 high-dose group of that study. Taken together, it
22 was apparent that these results on face suggested a

1 robust effect in the high-dose group of Study 302
2 and numerically intermediate effects that were
3 highly aligned in both low-dose groups.

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

15 The pattern of results I have just
16 described, however, was notable and demanded
17 further consideration. It was apparent that if the
18 results presented at that meeting did in fact
19 represent the true effect of aducanumab, it was
20 imperative that all efforts would be made to
21 understand how reliable the results were and to
22 achieve a maximum understanding of the data giving

1 rise to these results so as to determine both the
2 reliability and the impact of Study 301's results
3 on the interpretation of Study 302.

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

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

1 in-depth review of the protocols.

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

17 On June 14, 2019, the applicant had publicly
18 announced futility but recognized that subsequent
19 efficacy analyses based on data available through
20 March 20, 2019 diverged from the earlier assessment
21 of futility. Those additional analyses led the
22 applicant to seek a discussion with the agency of

1 the results of those analyses and the next steps to
2 be taken so that they would be taken with
3 appropriate regulatory considerations in mind.

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

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

20 Suggestions from the FDA provided in
21 responses sent to the sponsor in advance of the
22 meeting included suggestions to the sponsor,

1 including to explore whether there may be
2 demographic or baseline differences between studies
3 that contribute to the different results in the
4 high-dose group of each study and a request from
5 the FDA to provide conditional power estimates if
6 non-pooled futility analyses had been performed for
7 each study independently.

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

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

1 exposure, amyloid PET, and clinical endpoints.

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

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

19 Further complicating the interpretation of
20 the available data for Studies 301 and 302 were the
21 partially conflicting results for Study 301 as
22 compared with those for Study 302, with particular

1 attention to the discordant high-dose results of
2 each study, while at the same time noting an
3 apparent degree of consistency of the low-dose
4 results between the studies.

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

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

1 efficacy.

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

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

22 FDA noted that given the wholly unique

1 situation -- that is the current state of the
2 aducanumab development program, a large
3 international, apparently rigorously conducted,
4 logistically complex study that was near completion
5 but was now terminated with a public declaration of
6 futility and termination and with a large but
7 incomplete complicated and partially discordant
8 data set now suggestive of the possible
9 effectiveness of aducanumab -- further analyses
10 would best be conducted as part of a bilateral
11 effort involving the agency and the sponsor. The
12 agency and sponsor, the applicant, agreed to pursue
13 this approach.

14 An important initial step agreed to by both
15 parties was for the sponsor to arrange for the
16 prompt provision of the patient-level data sets to
17 the agency. FDA noted that depending on the
18 results of additional analyses of data for
19 Studies 301 and 302, when viewed in conjunction
20 with those analyses already available, the
21 submission of a marketing application for
22 aducanumab, based primarily on the results of

1 Study 302 as a single positive efficacy study, may
2 be considered and that currently available data do
3 not suggest the future use of Study 301 as an
4 efficacy study providing independent evidence of
5 effectiveness.

6 On October 21st, we had another Type C
7 meeting with the applicant noting that on June
8 14th, additional jointly agreed-upon analyses of
9 the results of Studies 301 and 302 had been
10 conducted by the agency and sponsor since that
11 time. Those analyses were intended to determine
12 whether early termination of Studies 301 and 302
13 may have impacted the interpretation of efficacy
14 data for those studies and to understand the
15 consistency of and differences in the efficacy
16 results of Studies 301 and 302. Based on these
17 analyses, the FDA agreed that the results of
18 Studies 301 and 302 were interpretable and suitable
19 for additional consideration.

20 Accordingly, and in the context of the
21 unique nature of the conclusion of Studies 301 and
22 302, the sponsor was informed that they had

1 presented on face the results of a trial of
2 aducanumab in the treatment of Alzheimer's disease
3 that met its primary endpoint. That would be
4 Study 302. Equally it was noted the sponsor had
5 presented on face the results of a trial of
6 aducanumab for the treatment of Alzheimer's disease
7 that did not meet its primary endpoint, Study 301.

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

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

1 exploratory exercise.

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

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

19 On February 27th of 2020, at this meeting to
20 discuss additional analyses and scientific
21 questions raised at the previous meeting, the FDA
22 noted that none of the analyses performed should be

1 viewed in isolation and none of the analyses were
2 intended to provide independent substantiation of
3 effectiveness. FDA noted that the analyses may
4 help provide an understanding of the overall data
5 for aducanumab and would be considered in terms of
6 their ability to support or undermine the
7 independent results of Study 302.

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

20 Talking about Studies 301 and 302 -- so I'm
21 going to assume that the slides are still not
22 working and neither is my computer -- Studies 301

1 and 302 were multicenter, randomized, double-blind,
2 placebo-controlled parallel group studies in
3 patients with early symptomatic Alzheimer's
4 disease, who are positive for brain amyloid
5 pathology as assessed by PET. Participants had to
6 have a baseline MMSE score of 24 to 30 and a CDR
7 global score of 0 to 5.

8 The study was conducted in 181 centers
9 globally. Randomization was stratified by site and
10 by ApoE4 carrier status, carrier or non-carrier, an
11 enrollment was monitored as such that 80 percent of
12 the population included patients with a baseline
13 clinical stage of MCI due to Alzheimer's disease.
14 The study included an 8-week screening period, a
15 78-week placebo-controlled treatment period, and a
16 safety follow-up period of 18 weeks after the final
17 dose.

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

1 special protocol assessment.

2 The declaration of futility was addressed
3 somewhat above, but when reviewing the regulatory
4 interactions, it warrants some additional comments.
5 An interim analysis for futility was prespecified
6 in the study protocols and the statistical analysis
7 plan to be performed after approximately the first
8 50 percent of participants in the studies had the
9 opportunity to complete the week 78 primary
10 efficacy assessment. The data cutoff date for the
11 prespecified futility analysis was December 26th of
12 2018.

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

20 The conditional power for each study was
21 calculated on a future estimate based on pooled
22 data from Studies 301 and 302. The conditional

1 power values were 12 percent for Study 302 and
2 0 percent for Study 301. As such, the probability
3 of a statistically significant difference was below
4 the prespecified cutoff of 20 percent. With the
5 futility criteria met on March 21st, the applicant
6 announced the termination of the aducanumab phase 3
7 program in accordance with the prespecified
8 futility analysis.

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

15 Because of this, after the futility
16 announcement and in response to a subsequent FDA
17 request, the conditional power was re-estimated for
18 the individual studies and futility was not met
19 using this non-pooled analysis. Therefore,
20 although the criteria for the futility analysis
21 were prespecified, the two key assumptions on which
22 the futility analysis was based were invalid and

1 results of the futility analysis yield inaccurate
2 predictions for the final outcomes.

3 Prior to the announcement of futility, the
4 studies continued to be rigorously conducted per
5 the clinical study protocols as planned under the
6 assumption that the studies would continue.

7 Therefore, at the time of futility declaration on
8 March 21st, a larger set of protocol compliant data
9 was available.

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

22 In May 2019, when the applicant first shared

1 the March 2019 ITT results with the FDA seeking the
2 agency's counsel and expert opinion on the
3 appropriateness and interpretation of the analyses,
4 it was immediately apparent, given the potential
5 import of the results, that it was critical to
6 determine whether the data were suitable for
7 analysis and interpretation given the premature
8 termination of the studies.

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

21 Overall, simulation results were highly
22 consistent with the primary analysis of the

1 observed data. Similar results were obtained using
2 all data or only data in patients who had the
3 opportunity to complete the week 78 visit. Based
4 on these results, the FDA and the applicant jointly
5 concluded that the early termination of the
6 aducanumab program did not compromise the
7 interpretability of the efficacy results of
8 Studies 301 and 302.

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

22 The results of Study 302 are highly

1 persuasive and the study appears capable of
2 providing the primary contribution to a
3 demonstration of substantial evidence of
4 effectiveness of aducanumab. The primary efficacy
5 endpoint analysis change from baseline and CDR-SB
6 at week 78 demonstrated a statistically significant
7 treatment effect in the aducanumab high-dose
8 treatment arm compared to placebo, as has already
9 been presented. The low-dose treatment arm
10 demonstrated a numerical advantage compared to
11 placebo but failed to reach statistical
12 significance with a p-value of 0.09.

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

20 The treatment benefit was observed across a
21 broad range of predefined relevant subgroups
22 defined by demography and baseline disease-related

1 characteristics. Study 302 was a strongly positive
2 study on multiple distinct and important clinical
3 measures, robust to numerous sensitivity analyses,
4 and supported by well-characterized biomarker data.

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

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

21 Study 301 failed to meet its primary and
22 secondary objectives. Neither treatment group of

1 Study 301 had statistically significant differences
2 from placebo in the primary efficacy endpoints or
3 the secondary efficacy endpoints. Study 301 is a
4 negative study.

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

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

22 Four areas were investigated to understand

1 the partially conflicting results in Studies 302
2 and 301: dose, baseline characteristics, ARIA, and
3 non-normality of the clinical data. By their
4 nature, these analyses were post hoc and
5 exploratory, and therefore carry with them the
6 appropriate caveats and caution in their
7 interpretation.

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

18 The purpose of these analyses was to provide
19 maximum understanding of the partially discordant
20 results and to determine if this understanding
21 precluded independent consideration of Study 302.
22 The FDA agrees that any differences in demographics

1 and baseline disease characteristics between the
2 studies are minor and do not appear to have a
3 meaningful impact on the outcome of the studies.

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

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

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

1 introduced by ARIA.

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

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

22 FDA agrees with the importance of dose in

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

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

21 A guiding principle of the hypothesis was
22 that if aducanumab is in fact effective and the

1 effect is dose related as in Study 302, it would
2 follow that patients in Study 301 with adequate and
3 consistent dosing should also demonstrate an effect
4 on clinical endpoints. An absence of an effect in
5 this subgroup of patients in Study 301 would
6 diminish persuasiveness of Study 302.

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

14 Additionally, in the Study 301 high-dose
15 group, clinical and biomarker outcomes were
16 impacted by lower exposures to the target dose of
17 10 milligram per kilogram. Fewer participants in
18 Study 301 had high exposure to 10 milligram per
19 kilogram and more participants had no exposure to
20 10 milligram per kilogram than in Study 302.

21 Although the precise relationship between
22 dosing and treatment effect is unknown, the

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

12 FDA also acknowledges the inherent
13 variability in clinical measures and challenges
14 measuring clinical decline in this patient
15 population. For these reasons, these analyses do
16 not provide independent evidence of the
17 effectiveness of aducanumab, but rather contribute
18 to an overall understanding of Study 301. Taken
19 together, multiple lines of evidence regarding both
20 similarities and differences between Studies 301
21 and 302 suggest the partially discrepant results
22 between Studies 301 and 302 are qualitatively

1 sufficiently well understood to allow for
2 independent consideration of the persuasiveness of
3 Study 302.

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

14 Doses studied in the first three cohorts,
15 which were arms 1 to 7, were 1, 3, 6, or
16 10 milligram per kilogram administered every
17 4 weeks, specifically 14 doses over the 12-month
18 placebo-controlled period. The randomization was
19 unequalled by arm and was stratified by ApoE status.
20 Participants in the fourth cohort, which is arms 8
21 and 9 comprising ApoE carriers only, were
22 randomized to either aducanumab or placebo during

1 the placebo-controlled period. Arms 8 and 9 were
2 added to Study 103 to assess whether the incidence
3 of ARIA can be mitigated in ApoE4 carriers by
4 titration.

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

17 Although design primarily is a safety and
18 tolerability study, Study 103 was a rigorously
19 designed placebo-controlled study that explicitly
20 included assessments of prespecified clinical and
21 biomarker endpoints and did have a prospectively
22 identified statistical analysis plan. Although not

1 prospectively controlled for multiplicity, the FDA
2 notes that the choice of endpoints and analytical
3 approach is consistent with that which would have
4 been anticipated should an analytical hierarchy had
5 been in place and that the prespecified elements
6 were respected.

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

16 However, the placebo arms were pooled across
17 cohorts in compliance with the prespecified
18 statistical analysis plan because of the uneven
19 randomization to placebo in each cohort within the
20 staggered design. The study informed the design of
21 Studies 301 and 302 but also included similar
22 elements as these studies, including the

1 requirements of a positive amyloid PET scan and
2 blinded assessment of clinical endpoints.

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

13 The clinical efficacy results of Study 103
14 were supported by a statistically significant
15 dose-dependent reduction in brain amyloid plaque as
16 measured by PET in comparison with placebo at
17 month 12, with a maximum reduction in the
18 10-milligram per kilogram fixed-dose group as
19 compared to placebo. The magnitude of the
20 reduction in brain amyloid plaques in the
21 10-milligram per kilogram group as compared to
22 placebo in Study 103 was extraordinarily similar to

1 that observed in the aducanumab high-dose group in
2 Study 302.

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

14 The statistical significance of the
15 10-milligram per kilogram treatment arm
16 demonstrated with both ANCOVA and MMRM analyses was
17 not robust to the exclusion of post-baseline
18 starting of Alzheimer's disease medications or
19 exclusion of the titration placebo arm. Despite
20 the smaller sample size, the 10-milligram per
21 kilogram dose arm was able to achieve nominal
22 statistical significance according to the

1 prespecified analysis plan. Also, the
2 dose-response relationships for A-beta reduction
3 provides support for the positive finding in the
4 10-milligram per kilogram treatment arm and are
5 consistent with the dose-response relationship
6 observed for CDR-SB and MMSE.

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

18 The estimate of the treatment effect in the
19 low-dose arm was numerically favorable and was
20 consistent with the dose-response relationship.
21 The treatment effects of the high-dose arm is
22 supported by consistently favorable results across

1 subgroups of interest. Biomarker results
2 demonstrate target engagement and treatment effects
3 on markers of Alzheimer's disease pathophysiology.

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

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

17 Study 301 is a negative study and does not
18 contribute to the evidence of effectiveness of
19 aducanumab. The results presented in support of
20 understanding the relationship of Studies 301 and
21 302 should not be interpreted as explaining why
22 Study 301 was negative. These analyses are

1 exploratory by design but limited in scope and
2 focused on predefined areas of interest.

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

9 An examination of dosing in Study 301
10 indicates that patients with higher exposure to the
11 10 milligram dose in Study 301 had similar
12 responses to patients in Study 302. These two
13 factors contribute to the overall understanding of
14 Study 301 and together do not meaningfully detract
15 from the persuasiveness of Study 302.

16 Substantial evidence of effectiveness is
17 required for approval. There is a need to
18 substantiate any individual finding to avoid
19 reliance on erroneous conclusions, so in general,
20 two independent studies are typically provided to
21 meet this need. An alternative approach can be
22 acceptable. Reliance on only a single study, a

1 single adequate and well-controlled efficacy study,
2 to establish substantial evidence of effectiveness
3 is a possibility in certain circumstances,
4 particularly when the disease in question is a
5 serious and life-threatening condition and the
6 effect is an important one to the disease.

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

20 Now, thinking of those characteristics and
21 with all things being equal, Study 302 would appear
22 to be a shining example of a compelling single

1 study, but all things may not be equal. We have an
2 unusual situation. We have one primary study, we
3 have support from a smaller study, futility was
4 declared, and we have a failed sister study.

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

15 We did that, and unbeknownst to us when we
16 did so, we were able to have an advanced start on
17 something that has affected neuroscience studies
18 more severely than any other therapeutic area,
19 interrupted trials that are happening because of
20 COVID. Our neuroscience trials are hard and
21 complex and they are struggling, and we are helping
22 with that with what to do with missing data and

1 restructuring trials midstream while attempting to
2 preserve their interpretability, and this is
3 recognized at the agency.

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

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

21 Dr. Stein noted that we are working --

22 DR. FOUNTAIN: Dr. Dunn, I just wanted to

1 let you know that you're a bit over your time. Of
2 course, it's your meeting. I'm just letting you
3 know to keep track of time because we might have a
4 bit for clarifying questions. Thanks.

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

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

18 Dr. Stein pointed out that the Office of New
19 Drugs is committed to helping sponsors overcome the
20 challenges caused by COVID-19. "We will be working
21 very cooperatively with sponsors, assessing what
22 kind of analysis can be done to make sure that the

1 data can be put together in a way that is
2 convincing and persuasive and lets us get to an
3 approval decision where appropriate."

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

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

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

20 If you'd like to ask a clarifying question
21 after now, you can put your hand up, and we'll
22 start with you, but we'll only have a few minutes

1 for clarifying questions, so if you could please
2 ask them very brief and to the point.

3 DR. DUNN: Just quickly, Dr. Fountain.

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

16 Support or undercut. What does 301 do to
17 302? We have chosen to be conservative and
18 consider only the latter, the undercut. There are
19 patterns in the data that given the failed nature
20 of the trial, our analyses are limited to
21 explorations. From our more recent effectiveness
22 guidance, findings from other trials that are not

1 consistent with the findings of the single positive
2 trial would need to be considered collectively and
3 could weaken the overall strength of evidence;
4 again, explicit instruction to consider the
5 inconsistent findings.

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

14 Indeed, that is part of the flexibility that
15 our regulations specify for the development of
16 drugs intended to treat life-threatening a severely
17 debilitating illnesses. While the statutory
18 standards of safety and effectiveness apply to all
19 drugs, the many kinds of drugs that are subject to
20 them and the wide range of uses for these drugs
21 demand flexibility in applying these standards.
22 The Food and Drug Administration has determined

1 that it is appropriate to exercise the broadest
2 flexibility in applying the statutory standards for
3 these conditions.

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

8 **Clarifying Questions to FDA**

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

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

19 The effect size of [indiscernible] -- the
20 amount of actual amyloid reduction in the 103 was
21 apparently much larger than in 302, and the
22 difference between amyloid reduction at the top

1 dose between 301 and 302 appears to be really,
2 really small. It would be helpful to try to
3 understand how with that pattern of data one can
4 view 103 being supportive of 302 and how one can
5 actually argue that a miniscule difference between
6 301 and 302 can explain such a whopping difference
7 in efficacy.

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

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

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

18 DR. GOLD: Oh, well --

19 (Crosstalk.)

20 DR. FOUNTAIN: We'll have a chance later to
21 ask, but if you want to direct that to the FDA to
22 respond to that --

1 DR. GOLD: I'm fine to direct it to the FDA
2 because as I understood Dr. Dunn, he believes that
3 103 is supportive of 302, so the question applies
4 to the FDA, too.

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

7 Dr. Krudys, would you take that? I had a
8 little trouble understanding him, but I think I
9 have the answer. I think Dr. Gold asserted that
10 103 had a much larger amyloid effect than 302.

11 Did you hear that also?

12 (No response.)

13 DR. DUNN: Dr. Krudys?

14 (No response.)

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

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

20 DR. GOLD: Yes. You had a reduction of
21 1.1 SUVR in 103 and only 0.27 SUVR reductions in
22 302. So the numbers that I have suggest that it

1 was much larger in 103 than in 302.

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

8 DR. GOLD: Okay.

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

18 It is notable that the amyloid effect is
19 lower. I think you see evidence in other
20 factors -- again, small numbers, exploratory
21 analysis, but you see some of the downstream
22 effects also being diminished. So there's an

1 overall pattern of diminution of response. But
2 again, I don't have those data. Dr. Krudys has
3 those data, and I want to make sure we check with
4 him if he's available.

5 DR. GOLD: Okay.

6 (Crosstalk.)

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

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

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

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

16 DR. GOLD: Okay.

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

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

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

1 related questions.

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

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

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

18 Dr. Krudys, are you online now?

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

21 DR. DUNN: Yes.

22 DR. KRUDYS: Can you hear me?

1 DR. DUNN: Yes.

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

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

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

11 So there is a small subset of the population
12 301 that is not consistent with what we would
13 expect from a dose-response relationship. But from
14 what we've seen in Studies 103 and 302, we do see
15 that if you increase the concentration of the
16 exposure, you're more likely to see a response. So
17 therefore, we look at the results in the high dose
18 of Study 301, and you see the patients who had the
19 highest exposure have a response that is similar to
20 that in Study 302.

21 I think if we didn't see that, it would call
22 to question the results that we saw in Study 302,

1 but we're seeing a consistent response at the
2 highest exposure. But there is, like I said, a
3 subset of patients who are in between first of
4 their exposure and don't have the response as we
5 would project based on the exposure-response
6 relationship we're seeing in Study 302.

7 DR. PERLMUTTER: Thank you for that. But as
8 a follow-up for that, if you tried to remove or if
9 you removed rapid progressors from the analysis in
10 301 and then you find it changed, how do you do
11 that prospectively? Isn't that always for the
12 treatment, is follow up how much they've changed?
13 How would that even be implemented?

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

18 Can we save that for the discussion session?

19 DR. PERLMUTTER: Okay. Thank you.

20 DR. FOUNTAIN: Okay.

21 Dr. Kryscio, I see you've put your hand
22 down, so I'm assuming there's not a question. And

1 we have time for one more question in this session,
2 and I believe next in order would be Dr. Emerson.

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

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

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

16 But you remarked that the assumption of a
17 common treatment effect was violated in the
18 futility rule. If that's the case, how will you
19 distinguish between the population that was in 302
20 and therefore has a treatment effect and the
21 population in 301 that apparently does not have a
22 treatment effect?

1 I'll note that the futility analysis
2 presumed that there would be differences in the
3 estimated treatment effect, and that is why
4 presumably they chose to use the combined groups to
5 try to get a better estimate. So your statement
6 that the treatment effects common between the two
7 groups is violated argues that we should not write
8 an indication that encompasses both study
9 populations.

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

13 DR. EMERSON: Again, if you are saying that
14 the futility analysis was wrong because there was
15 an assumption of a common treatment effect for both
16 studies and that that was violated, that must mean
17 that your belief that the treatment works in the
18 302 population but doesn't necessarily work in the
19 301 population must be somehow taken into account
20 as you write an indication for this drug. How will
21 you do that?

22 DR. DUNN: Yes. I think that the point that

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

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

13 DR. EMERSON: So the FDA statistician, who
14 we haven't heard from in this meeting but who did
15 write a very nice report, might also bring to bear
16 on this about what the distinction is between a
17 treatment effect common between the two studies and
18 similar estimates of treatment effect between the
19 two studies and the difference between those.
20 Which of those were assumed in the futility rule
21 and which of those need to be assumed for issuing
22 the general indication for all patients?

1 (No response.)

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

4 DR. MASSIE: Hi. This is Tristian. Can you
5 hear me --

6 DR. EMERSON: Now, I can. Thanks.

7 DR. MASSIE: -- the FDA a statistician.

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

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

14 DR. EMERSON: Again, my question is -- and
15 I'd be interested in your opinion -- in terms of
16 using conditional power, which I think is a poor
17 choice for a variety of reasons just because of
18 understanding the futility rule. But in using
19 conditional power, my presumption would be the
20 motivation for combining the treatment estimates
21 across the two studies would be to get a more
22 stable estimate to use in the conditional power

1 calculation under the assumption that there would
2 be differences in the estimate, but they were
3 estimating the same treatment effect. It is a
4 major scientific question if you are presuming that
5 there is a different treatment effect, the true
6 treatment effect between these two studies.

7 Is my reasoning in agreement with what you
8 would say?

9 DR. MASSIE: Yes. I think, a priori, it
10 makes sense to have a more stable estimate when you
11 have two identically designed studies and you're at
12 50 percent in both. So if they're identically
13 designed, if you combine them to get a more stable
14 estimate, that makes a lot of sense.

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

20 Is that acceptable to you, Dr. Emerson?
21 Does that essentially answer the specific question?

22 DR. EMERSON: Yes. Thanks.

1 DR. FOUNTAIN: Thank you.

2 Alright. That ends the clarifying questions
3 for the FDA. We'll now break for lunch. We will
4 reconvene in one hour, a little less than one hour,
5 55 minutes, at 1:30 p.m. Eastern time. Panel
6 members, please remember that there should be no
7 chatting or discussion of the meeting topics with
8 other panel members during the lunch break.
9 Additionally, you should plan to rejoin at around
10 1:15 to ensure you're connected before we reconvene
11 at 1:30. And just as another parenthetical note,
12 of course you can remain on the Adobe Connect as
13 well.

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

15 Thank you.

16 (Whereupon, 12:36 p.m., a lunch recess was
17 taken.)
18
19
20
21
22

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

(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

1 meeting.

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

9 The FDA and this committee place great
10 importance in the open public hearing process. The
11 insights and comments provided can help the agency
12 and this committee in their consideration of the
13 issues before them. That said, in many instances
14 and for many topics, there will be a great variety
15 of opinions.

16 One of our goals for today is for the open
17 public hearing to be conducted in a fair and open
18 way, where every participant is listened to
19 carefully and treated with dignity, courtesy, and
20 respect. Therefore, please speak only when
21 recognized by me, the chairperson. Thank you for
22 your cooperation.

1 Each of the open public speakers will have
2 three minutes for their presentations.

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

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

17 When I was first diagnosed with Alzheimer's
18 disease in 2016 at the age of 51, I quickly
19 resolved myself to the prognosis of the disease and
20 immediately took steps to confront this monster and
21 enrolled in the aducanumab trial. I understand
22 that Biogen needed to make a decision to halt the

1 trial based on a futility analysis, however, it is
2 difficult to express my overwhelming sense of
3 gratitude that in October of 2019, the same year,
4 we were notified the trial was going to be reopened
5 for reenrollment as the EMBARK study with a goal to
6 move forward to FDA approvable.

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

19 My wife and family often say that we can
20 live with the damage that has been done to my brain
21 from Alzheimer's as long as I can live longer. In
22 many cases with the diagnosis of younger onset of

1 Alzheimer's disease, the person is face was just a
2 few years. I'm coming up on my fifth year with my
3 three kids graduating from a university and
4 celebrating my middle daughter's quality-of-life
5 milestones and bucket-list items we thought we
6 would miss. We believe that grandchildren will be
7 the next milestone bucket-list items and no small
8 part to the much needed aducanumab medication.

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

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

1 DR. FOUNTAIN: Thank you.

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

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

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

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

22 The pivotal trials were terminated early

1 after the prespecified interim analysis for
2 futility and showed only EMERGE was turning
3 positive, whereas ENGAGE was unlikely to meet its
4 primary endpoint. A subsequent post hoc analysis
5 of the trials showed that in EMERGE, high-dose
6 aducanumab followed improvement in the primary
7 efficacy endpoints, but in ENGAGE, no benefit with
8 low- or high-dose aducanumab. Such post hoc
9 analyses are highly susceptible to bias, do not
10 provide substantial evidence of effectiveness, and
11 should only be used to generate hypotheses for
12 possible future trials.

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

19 Contrary to FDA's assertion, the EMERGE and
20 ENGAGE data also must be assessed in the context of
21 the two-decade history of 22 other failed drugs
22 targeting amyloid-beta accumulation, including five

1 other anti amyloid-beta monoclonal antibodies, many
2 of which caused harm. See this table. In this
3 historical context, which called into question the
4 amyloid hypothesis, there is a significant
5 probability that the EMERGE efficacy results
6 represent a false positive.

7 FDA's statistical reviewer Tristian Massie
8 correctly highlighted the lack of substantial
9 evidence of effectiveness for aducanumab. In this
10 case, we do not have a single strong study in
11 isolation. On the contrary, we actually have a
12 second trial in which the purported effective dose
13 was in the wrong direction compared to placebo.
14 Under the null, if winning in just one study out of
15 two was enough, then there's a chance that falsely
16 rejecting the null would be 0.0975 across the two
17 studies. Furthermore, if we select only the better
18 study, our estimate is very likely biased and we
19 already know not consistently repeatable. Thus,
20 excluding data from a large trial without
21 sufficient justification is unscientific,
22 statistically inappropriate, and misleading.

1 My last slide. In closing, FDA must demand
2 another premarket, randomized, placebo-controlled
3 trial of aducanumab. FDA approval of the drug
4 would further damage the agency's already
5 diminished credibility. We therefore urge the
6 committee to vote no on question 7 and recommend
7 that FDA not approve this drug. Thank you.

8 DR. FOUNTAIN: Thank you.

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

13 MS. TAYLOR: My name is Geri Taylor.

14 MR. TAYLOR: And my name is Jim Taylor.
15 Geri and I have twice spoken to Biogen employees.
16 We were paid several hundred dollars, funds
17 subsequently donated to Alzheimer's research. With
18 her nursing experience, Geri is a trained observer.
19 With her research background, in the 1970s, she
20 co-authored the very first article on the
21 importance of medical second opinions in the New
22 England Journal of Medicine. As the COO of the

1 largest long-term care health facility in New York
2 City, Geri oversaw dementia and hospice facilities.
3 As an ApoE double-4 carrier, she has witnessed the
4 impact of Alzheimer's on both parents.

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

12 Geri participated in Study 103 at the
13 10-milligram dosage for over four years.
14 Ironically, on the day that the trials were
15 terminated, I was in Bethesda, Maryland serving as
16 the patient representative at an FDA Alzheimer's
17 public hearing. Being ineligible to serve today
18 because of Jerry's trial participation, I well
19 remember the preparation time and challenging
20 deliberations required. Geri and I thank each of
21 you for your participation today.

22 Aducanumab's termination was especially

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

10 Anecdotal, of course, but we believe
11 representative of those Study 302 participants on
12 10-milligram dosage for 18 months, whom we know
13 experienced significant slowing and cognitive and
14 functional decline. Even if only some individuals
15 respond to treatment, aducanumab will be a
16 tremendous ray of hope for those who today, with no
17 meaningful disease-modifying therapy, live
18 difficult lives. Geri joins me in urging you to
19 approve aducanumab. Thank you.

20 MS. TAYLOR: Yes, thank you.

21 DR. FOUNTAIN: Thank you.

22 Speaker number 4? Speaker number 4 is now

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

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

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

21 In January of 2017, he received his first
22 aducanumab infusion. He responded beautifully for

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

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

22 Kevin began to have significant deficits in

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

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

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

1 and to have hope once again as we do. Thank you.

2 DR. FOUNTAIN: Thank you.

3 Speaker number 5, your audio is connected.

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

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

17 As a leading voluntary health organization
18 in Alzheimer's care, support, and research, each
19 year we speak with hundreds of thousands of
20 families through our 24/7-365 help line and serve
21 hundreds of thousands more, providing access and
22 direct support to people living with this disease

1 and their families and communities across America.
2 Through our work, we see firsthand, every day, the
3 devastating toll Alzheimer's disease takes on
4 individuals, their caregivers, and families.

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

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

19 That is why the decision before the members
20 of this committee is so critical. The need for
21 relief for millions of Americans impacted each day
22 by the crushing realities of Alzheimer's is

1 overwhelming. Given the devastating toll of this
2 disease, the publicly released data justify
3 approval accompanied by a face for postmarketing
4 surveillance study. Requiring completion of an
5 additional phase 3 trial would deny access up to
6 four years while it is completed. A four-year
7 delay is too long for too many. The potential to
8 delay decline would be denied to millions and the
9 potential to say damage and death for some
10 caregivers is real.

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

22 DR. FOUNTAIN: Thank you.

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

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

21 As everyone knows, Study 302 was positive
22 with the high-dose treatment and Study 301 was

1 negative and actually favored placebo. Blinding is
2 always very important in a randomized double-blind
3 study, and since a large number of patients, almost
4 half, had ARIA, I want to just mention, although
5 there was a mitigation where raters were
6 independent of patient care and so remain blinded,
7 the patient's weren't blinded. They certainly,
8 many of them, would have been suspicious because
9 they were treated differently to manage these side
10 effects.

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

18 Nevertheless, I completely agree with FDA's
19 statistical concerns that were expressed in
20 Dr. Massie's slides. Inconsistency, they wrote
21 that, "We have a equally sized and identically
22 designed Study 301 that directly contradicts 302,

1 and the 301 high dose is numerically worse than
2 placebo," and then there are concerns about the
3 null hypothesis.

4 Here are other quotes from the FDA slide.
5 "If you have two studies and you take the best and
6 pretend like it's the only one, their estimate is
7 likely biased." Another quote, "At best, evidence
8 is from 302 only and there exists conflicting,
9 adequate, well-controlled evidence."

10 DR. FOUNTAIN: Is this the last slide?

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

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

14 DR. ZUCKERMAN: Sure.

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

20 So you have a really tough decision today
21 because there's an urgent desperate need for
22 treatment, but the family dilemmas are going to be

1 that this treatment, if approved, is going to be
2 extremely expensive, and it will not be clear who
3 it might work for, so some families will really
4 lose all their savings in order to hope that the
5 treatment works for them.

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

12 DR. FOUNTAIN: Okay.

13 (Crosstalk.)

14 DR. ZUCKERMAN: Thank you very much.

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

17 Speaker number 7, your audio --

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

20 DR. FOUNTAIN: No, go ahead.

21 MR. VRADENBURG: My name is George
22 Vradenburg, chairman of UsAgainstAlzheimers, a

1 patient-led nonprofit with the single mission to
2 stop Alzheimer's. We're supported in that mission
3 by thousands of individuals and scores of
4 companies, including Biogen.

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

13 What matters to us? We know from our own
14 statistically rigorous studies what matters most,
15 that all 10 of the things that matter most to those
16 early in the Alzheimer's journey are embodied in
17 the clinical endpoints in the aducanumab trial.
18 But for us, for example, and ADL scale is not just
19 an endpoint, it's more weeks and months and maybe
20 years of living independently; of being safe when
21 left alone; of being able to use the shower or the
22 toilet.

1 To get to the best-in-class drug, a cure, we
2 must have a first-in-class drug because we have
3 learned. With so many other
4 challenging diseases, all of us who have been
5 through cancer know there's no sure thing and side
6 effects can be brutal. But those of us with early
7 Alzheimer's aren't afraid of headaches for goodness
8 sake; we're on the path to dying.

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

18 For us, waiting for perfection is not an
19 option. We're losing the ability to recognize our
20 family members now. We're becoming agitated now.
21 We are losing ourselves now. We simply can't wait.
22 The signal you send today will have a ripple effect

1 far beyond this one drug. The signal you send
2 today can stop the path to a cure for years or
3 correct the sound of the starting gun on
4 innovation.

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

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

20 DR. FOUNTAIN: Thank you.

21 Speaker number 8 is connected to the audio.
22 You may begin.

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

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

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

22 When he was finally diagnosed, we were told

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

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

16 So I ask the committee, what is time worth
17 when you're tethered to a diagnosis where you
18 slowly lose your intellect, independence, and the
19 very essence of who you are as an individual?
20 Those who are eligible must be given the chance to
21 buy time. Let them work with their physicians to
22 decide if the risk is worth its potential.

1 The unmet need is obvious. Please take
2 every measure to bring this therapy forward. We
3 don't expect guarantees. All we ask is the chance
4 for more time upfront and ahead of our fate. That
5 for millions of patients and their families is
6 clinically meaningful. Thank you for your time.

7 DR. FOUNTAIN: Thank you.

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

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

18 The disease took my maternal grandfather, my
19 mother, paternal uncle, and before my father's
20 death, he too was diagnosed with dementia. Then it
21 came for me. I was diagnosed about nine years ago
22 with early Alzheimer's after experiencing the

1 horrific trademark symptoms, and after two serious
2 head traumas, the doctor said I mask the disease in
3 the making. I also carry the Alzheimer's gene
4 ApoE4. I'm 70 now.

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

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

1 time in the moment with our families.

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

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

14 DR. FOUNTAIN: Thank you.

15 Speaker number 10, your audio is connected.

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

1 trials for Alzheimer's.

2 I was the lead author on the first report of

3 ARIA in 2009 and I'm an expert in ARIA management.

4 I have no significant financial interest with the

5 sponsor or others. I'm speaking on behalf of my

6 patients at this meeting, and I prepared these

7 remarks on my own without consultation with Biogen.

8 I want to thank the thousands of courageous

9 study participants who contributed to the data

10 under review today. Aducanumab produced a

11 significant dose-dependent lowering of amyloid

12 plaques in all studies and the slowing of cognitive

13 decline in two out of three trials. ARIA when

14 present was typically transient and manageable with

15 careful titration and safety monitoring.

16 Could I have my slides, please?

17 I was a site PI for the PRIME and ENGAGE

18 trials and I treated more than 60 patients on

19 aducanumab with many on open treatment for more

20 than five years. We follow our patients closely

21 and I'm well aware of changes in their daily

22 functioning. Overall, patients on open treatment

1 with aducanumab declined less than expected over a
2 period of years.

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

18 We are at a critical juncture in Alzheimer's
19 treatment. Too many memories will be lost if we
20 have to wait four to five years to complete a new
21 trial. The positive benefits of aducanumab clearly
22 outweigh the certainty of decline if this treatment

1 is not approved. Approval of aducanumab will be
2 associated with many firsts for Alzheimer's: the
3 first drug approved in 17 years; the first approval
4 for MCI due to AD; and the first treatment
5 targeting a core pathology disease.

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

13 DR. FOUNTAIN: Thank you.

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

18 MR. BRISTOL: Hi. I'm Peter Bristol. I'm
19 representing myself. I have no conflict of
20 interest, and I'm definitely honored to be here
21 today. In my opinion, Biogen's aducanumab should
22 be an Alzheimer's disease therapy.

1 I'll present my statement based on my
2 experience and will share my passion to see a cure
3 for AD. I have a family history of Alzheimer's
4 disease and dementia and my forgetfulness was
5 limiting my effectiveness at work. After my
6 mother, uncle, and most recently my brother died
7 with AD, I took the initiative to see the
8 preeminent Alzheimer's and dementia researcher, as
9 you heard, Dr. Stephen Salloway at Butler Hospital.

10 I was eligible and joined the A4 study. The
11 A4 study is a phase 3 clinical trial for
12 cognitively normal older adults whose brain scans
13 show evidence of amyloid buildup, which places them
14 at risk for memory loss and cognitive decline
15 associated with Alzheimer's disease. Three
16 motivators, hope, trust, and commitment, helps many
17 other trial participants and helped me persist
18 through the initial four-and-a-half-year trial and
19 my current four-year, open-label extension.

20 Hope, hope that by participating in a trial
21 I will find a cure for AD and maybe even have any
22 of my further cognitive decline slowed or stopped.

1 Trust, trust that I will be treated safely
2 and respectfully, which I am.

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

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

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

1 DR. FOUNTAIN: Thank you.

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

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

16 About 10 to 12 years ago, my husband David,
17 a nurse, noticed that I was experiencing cognitive
18 challenges such as double-booking airline flights,
19 duplicating of bill payments, memory issues,
20 concentration issues, and word searching. There
21 were many visits to the doctors and urologists and
22 I participated in several memory tests about nine

1 years ago. There were challenges with my insurance
2 company paying for MRIs, amyloid and tau PET scans,
3 and spinal taps.

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

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

21 I share this journey with you to identify
22 the years that I have passed since initial onset,

1 testing, and diagnosis. Biogen now has a drug
2 therapy that has successfully passed clinical
3 trials and the drug has clear signs that it works
4 as intended. A therapy of this nature that I and
5 many others, and my care partners, strongly support
6 provides an opportunity to slow down my cognitive
7 decline.

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

18 I'm an active advocate and advisor with the
19 Alzheimer's Association and I want to continue with
20 that path to provide awareness. I request the FDA
21 to approve the therapy and to do so quickly for the
22 benefit of myself and millions of others in the

1 United States just like me. Thank you for the
2 opportunity and comments.

3 DR. FOUNTAIN: Thank you.

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

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

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

1 aducanumab for patients with MCI and mild
2 Alzheimer's disease.

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

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

21 Patients with mild cognitive impairment are
22 even more therapeutically orphaned. There is no

1 approved therapy for patients diagnosed with MCI.
2 Millions of patients receive this devastating
3 diagnosis without access to an FDA-approved therapy
4 tested and measured for fitness for their
5 condition. Approving this drug will offer hope,
6 catalyze advanced blood tests, and encourage
7 diagnosis of the disease earlier and more
8 effectively. And frankly by definition, aducanumab
9 merits approval for MCI. It demonstrated
10 significant effectiveness in treating the condition
11 that afflicts millions of Americans that have no
12 alternative therapy.

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

22 In conclusion, aducanumab offers real

1 clinical benefits to millions of AD patients who
2 currently are devoid of a meaningful therapy.
3 Additional delay is unwarranted. We strongly
4 encourage the committee to recommend its approval.
5 Thank you.

6 DR. FOUNTAIN: Thank you.

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

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

15 I have early stage, early onset Alzheimer's.
16 I was diagnosed in 2016 after many, many months of
17 cognitive testing, brain scans, and MRIs. My
18 symptoms actually started in 2014, but
19 unfortunately my doctors dismissed my symptoms
20 because I was so young. It wasn't until my husband
21 accompanied me to an appointment with my
22 neurologist and shared stories of me repeating

1 myself and not remembering conversations that we
2 finally got some help. I live in the Bay area, and
3 thankfully UC San Francisco's research department
4 was able to confirm my diagnosis. I don't have a
5 family history of dementia, so when I started to
6 experience changes in my memory and thinking,
7 Alzheimer's wasn't on my radar.

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

17 I wish I could say that this diagnosis
18 brought relief to my family, but there was none.
19 We are one of those close, boisterous families and
20 together we cried and cried. They shared their
21 disbelief and their overwhelming grief at the
22 thought of my eventual decline. I hate to think of

1 the pain and sadness this disease will inflict on
2 them as I start to deteriorate and need more help.

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

14 There are many, many stories like mine
15 across this country, many men and women hoping and
16 praying for a cure or to be selected for a clinical
17 trial that could potentially slow down the
18 progression of the disease. It's time for those of
19 us living with Alzheimer's to hear some good news.

20 We need hope that there will one day be a
21 cure. We need hope that there will be a drug
22 treatment that can slow down progression. We need

1 hope that the 5.8 million people living with
2 Alzheimer's have faith that drug trials can and
3 will make a difference for them and their family.
4 Thank you for this opportunity to speak with you.

5 DR. FOUNTAIN: Thank you.

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

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

19 At the time of my diagnosis, I was a sitting
20 superior court judge here in California. My job in
21 a nutshell was to make decisions for the parties
22 appearing before me as to how to resolve disputes

1 that had arisen between them which they could not
2 resolve on their own. As a result of my diagnosis
3 of Alzheimer's, I was compelled to resign my
4 position and retire early rather than risk
5 challenges to my decisions based on any assertion
6 of lack of mental competence arising from my
7 condition.

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

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

1 undiagnosed.

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

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

10 JUDGE BROOKS: Yes, it is.

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

13 Next is speaker number 16. Speaker number
14 16, will you introduce yourself? State your name
15 and any organization you're representing for the
16 record.

17 MS. WHITING: Hi. Good afternoon. My name
18 is Grace Whiting, and I am the president and CEO at
19 the National Alliance for Caregiving. We're a
20 501(c)(3) nonprofit organization and coalition in
21 the DC area, and our mission is really to build
22 partnerships in research, advocacy, and innovation

1 that can make life better for family caregivers.

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

9 I also would like to disclose that Biogen is
10 a current member of the National Alliance for
11 Caregiving. In FY2019, they contributed membership
12 dues as did several other corporations and
13 not-for-profit organizations. Those dues were
14 roughly 2 percent of our total revenue, and we
15 anticipate that they will renew their membership
16 this year and that income will be approximately
17 1.6 percent of our total revenue.

18 I'll also mention that there's more detail
19 in a written comment that we submitted, but I'd
20 like to highlight a couple of key things when
21 you're thinking about this issue. The first is I
22 just want to say thank you. Thank you for thinking

1 about caregivers. Thank you for the work that the
2 FDA has done in June of this year talking about the
3 caregiver's role in medical product development.

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

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

1 on the family?

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

13 **Questions to the Committee and Discussion**

14 DR. FOUNTAIN: Thank you.

15 The open public hearing portion is meeting
16 has now concluded. We will no longer take comments
17 from the audience. The committee will now its
18 attention to address the task at hand, the careful
19 consideration of the data before the committee, as
20 well as the public comments. I want to take a
21 moment to just personally express my gratitude for
22 all those who came forward for the public comments.

1 I recognize sometimes those are difficult things to
2 say in public and to recognize, and it's very much
3 appreciated by the committee.

4 We'll now turn our attention to the
5 questions at hand. I'd like to remind public
6 observers that while this meeting is open for
7 public observation, public attendees may not
8 participate except at the specific request of the
9 panel. I'll open the question to discussion.

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

20 So before we discuss the specific content,
21 the question, before we discuss all this, is there
22 any issue that needs to be raised or clarified

1 about the wording of this discussion point?

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

7 Alright. Dr. Alexander?

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

9 DR. FOUNTAIN: Yes.

10 DR. ALEXANDER? Okay. I wanted to ask a
11 question of the FDA earlier, and it's relevant to
12 this question. I guess the bottom line is that I
13 find the materials that the FDA has provided
14 strikingly incongruent, and I have a very hard time
15 understanding, after carefully reviewing, what I
16 thought was a very well done and well articulated
17 biostatistical review, which convincingly argued
18 the evidence was, quote/unquote, "At best,
19 compelling include that there are substantial
20 evidence of effectiveness," and in particular that
21 Study 302 provides, quote/unquote, "a robust and
22 exceptionally persuasive study."

1 It just feels to me like the audio and the
2 video on the TV are out of sync, and there are
3 literally a dozen red threads that suggests
4 concerns about the consistency of evidence, a
5 dozen. For every point that you can find
6 suggesting support, there's another point or two
7 that raises concerns. So there's only one time
8 point with statistically significant different
9 findings from placebo. Forty percent of the ITT
10 analysis didn't have the opportunity --

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

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

22 There have been some very good questions

1 about this already that highlight the inconsistency
2 of findings across these three studies. So I
3 understand the question, but I'm not convinced that
4 this is where we should be focusing our time.

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

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

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

16 DR. FOUNTAIN: Sure.

17 DR. EMERSON: They ask us to talk about 302
18 by itself, which I can do, but it has to take into
19 account that this is the most exciting of results
20 of two studies, and I need to make certain that the
21 FDA is aware of that as they ask this question.
22 And then part of this, I guess we could ask

1 Dr. Dunn to tell us what he thinks the p-value is
2 from the primary analysis in 302, and this will
3 tell me a lot about whether he's thinking that 302
4 independent of 301 means pretend that 301 was never
5 done or whether it means adjust the inference to
6 allow for the fact that this is the best of two
7 studies.

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

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

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

22 DR. FOUNTAIN: So that's the nature of the

1 question, and I think maybe we could save that for
2 the discussion about whether or not that's --

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

14 DR. FOUNTAIN: Okay. So you --

15 DR. EMERSON: -- [indiscernible].

16 (Crosstalk.)

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

22 DR. EMERSON: Well again, we can talk about

1 the sampling of 302, what the true sampling
2 distribution was for 302, or we could talk about
3 302 with 301, taking both results. One result is
4 saying 302 is the best of two possible studies.
5 That's one sampling distribution. Another is
6 saying we're going to look at 302, just the 302,
7 and recognize that 301 carries the exact same
8 weight and eventually would be taken care of in a
9 meta-analysis.

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

1 he taking into account the erroneous conclusion
2 that that was a p-value of 0.024.

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

8 DR. DUDA: I have an independent question.

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

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

17 DR. FOUNTAIN: Okay. So you'd like a
18 qualifier before treatment of Alzheimer's disease,
19 the treatment of the symptoms of Alzheimer's
20 disease, or treatment of the pathophysiology of
21 Alzheimer's disease, or treatment of the
22 progression of Alzheimer's disease? Is that the

1 kind of thing you're asking about?

2 DR. DUDA: Yes, that would be helpful.

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

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

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

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

16 DR. GOLD: Yes. I have a particular issue
17 with the viewed independently and without regard
18 for 301 since those studies are identical in
19 design, identical in inclusion/exclusion criteria,
20 and identical presumably in biomarker analysis. So
21 I have real serious issues with how you can divorce
22 the two studies from each other.

1 DR. FOUNTAIN: Okay. The question, you
2 would like to us -- I'm having trouble what it is
3 we're going to ask --

4 DR. GOLD: You can do it independently --
5 (Crosstalk.)

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

10 DR. GOLD: Correct.

11 DR. FOUNTAIN: -- understand that.

12 DR. GOLD: Thank you.

13 DR. FOUNTAIN: Dr. Kryscio?

14 DR. KRYSCIO: I'm going to reserve my
15 questions for a little bit later on when we get to
16 103.

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

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

1 had. I just want clarification.

2 DR. FOUNTAIN: I think that's correct. Yes.
3 The question's to discuss the evidence, so that
4 means the evidence we know about, of the
5 effectiveness, as we know effectiveness, to be
6 provided by Study 302 -- that's the study called
7 302 -- viewed independently without regard for
8 Study 301 -- that's the other study -- with
9 particular consideration of the size of the study
10 and these other issues. The question is, is the
11 question clear and can we do that?

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

1 Does someone have a specific point of
2 clarity?

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

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

18 (Crosstalk.)

19 DR. FOUNTAIN: I think that's pretty clearly
20 the nature of the question. I think the nature of
21 the question is pretend like 301 -- in your
22 wording, pretend like 301 didn't exist and just ask

1 about 302, because in the subsequent questions
2 we're getting clarity on that, and then a
3 consideration is how does that change your mind.

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

20 DR. FOUNTAIN: So I think your position is
21 clear. I think we have to answer the question
22 we're asked, and then we can discuss in our voting

1 how we voted and how that influenced our vote.
2 Because if we just eliminate the question, I don't
3 think that will be helpful. I think the reason for
4 the questions and discussion are to get at those
5 kinds of points to make clear what we think. So I
6 think we just have to clearly understand what
7 they're asking whether you agree or like it or not
8 because then we have the opportunity in the voting
9 to decide what we think of that.

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

17 So now we have trouble discussing this
18 because it's all being supplanted by saying look
19 over here and answer this irrelevant question, and
20 we aren't really going to give you the opportunity
21 to say how this study should be interpreted if we
22 want to ignore the numbers from 301, but we may

1 never, ever, ever, ever ignore the fact that 301
2 was done.

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

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

18 DR. FOUNTAIN: Okay. We can discuss that
19 here and then vote because I don't think we're
20 going to be able to get to the voting unless we do.
21 So I think we should have some open discussion on
22 this question, among others, and I think we've

1 heard clearly so far that there is an idea that 302
2 can't be viewed without thinking 301.

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

5 (No response.)

6 DR. FOUNTAIN: Comment?

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

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

12 DR. FOUNTAIN: Yes.

13 DR. THAMBISETTY: So I completely understand
14 the points that Dr. Emerson and Dr. Alexander have
15 made, and in fact I shared a similar concern. But
16 I take some measure of comfort from discussion
17 number 7 and its accompanying both because I think
18 that sort of gets to the point that we are trying
19 to resolve here, because in the text for discussion
20 7, we are clearly allowed to discuss the impact of
21 the results of Study 301 on the consideration of
22 the results of Study 302.

1 (Automated interruption.)

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

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

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

9 DR. FOUNTAIN: Yes, we hear you.

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

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

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

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

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

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

20 DR. FOUNTAIN: Yes.

21 DR. THAMBISETTY: I share the satisfaction
22 and the concern about the wording of this question,

1 but I take some measure of comfort from the text
2 for discussion point number 7, which to me looks
3 that it gives us ample opportunity to discuss the
4 impact of Study 301 on the results of Study 302.

5 I know that. So as I have said, I hope I'm
6 not speaking out of turn, but I think there is
7 going to be ample opportunity for us to discuss 301
8 and 302 together.

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

15 DR. THAMBISETTY: Yes.

16 DR. FOUNTAIN: I think the nature of this
17 question is it would say -- I read this question to
18 be, if you look at Study 302, is it a positive
19 study? And in my view, yes, it's a positive study
20 because it's designed well, analysis looks
21 appropriate, consistency in the results, et cetera,
22 if you view it in isolation. If there was a single

1 study as was intended prospectively designed, that
2 makes it positive, unless you have concerns about
3 stopping early and so forth, or something about the
4 way it's analyzed.

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

14 I think Dr. Alexander is next.

15 (No response.)

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

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

20 DR. FOUNTAIN: Yes.

21 DR. ALEXANDER: Thank you.

22 So I will speak only to 302 and resist the

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

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

22 A fifth is that, as was pointed out by the

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

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

19 (Crosstalk.)

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

21 DR. GOLD: Yes. I'm assuming we're already
22 in the discussion. I think part of my concerns

1 about 302, if I talk about it in isolation, is what
2 happened pre- and post-amendment and the actual
3 numbers of subjects. And again, I'm sorry; 301
4 comes into it because it's a question of who was
5 being enrolled and what happened.

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

16 I just would like to get more clarity on
17 exactly how the amendment really impacted 302
18 because if you think about it, the amendment only
19 impacted ApoE4 subjects at the highest dose, but
20 there's evidence from looking at the ITT analysis
21 and for the post-Amendment 4 population that was in
22 effect on the low dose in the 302 study, which

1 makes absolutely no sense to me. And again, it's
2 material that that Biogen presented at CTAD.

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

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

19 So it would be helpful to understand whether
20 the analyses and the effect -- really, do we
21 actually believe that these data are missing at
22 random? Because that seems to be the assumption

1 that was made in the analyses, where the FDA
2 reviewer was clearly saying, hey, there are red
3 flags here that these data are missing not at
4 random. So I'd like to get some clarity on some of
5 those questions since we're already into the
6 discussion of the study itself.

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

10 DR. ALEXANDER: Correct.

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

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

22 DR. FOUNTAIN: Okay.

1 Next, Dr. Duda?

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

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

18 Next is Dr. Kesselheim.

19 DR. KESSELHEIM: Hi. Some of the points
20 that I was going to raise have been raised by
21 others, but I just wanted to also make the point
22 that analysis of this question is challenging for

1 me because we wouldn't be analyzing Study 302 in
2 isolation unless 301 existed because 302 is half,
3 or even at best two-thirds of a study. It was
4 stopped for futility. And if it would have existed
5 by itself, it would have never been stopped for
6 futility. It would have been continued until the
7 final results were in. So it's strange to rely on
8 half or two-thirds of a study as your evidence of
9 effectiveness for a drug.

10 DR. FOUNTAIN: You mean about 302 or 301?

11 DR. KESSELHEIM: 302. Sorry.

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

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

1 about.

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

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

14 Just to make clear, I do have a medical
15 degree, but I am a biostatistician. But more
16 importantly in this, I have family members who had
17 very severe Alzheimer's, and I've watched my
18 mother-in-law degenerate from a very vibrant person
19 to somebody who is just a complete invalid over a
20 space of 18 years. So I understand what there is,
21 and that does influence whether I would take the
22 0.023 -- or 0.24, and this is best probably a

1 minimum p-value that's there.

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

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

20 The internal consistency of the secondary
21 endpoints, we saw for about two seconds a slide
22 about the principal components analysis that I was

1 just trying to figure out, and they quickly say
2 "slide down" and it goes away. But some of the
3 points that they were trying to make are partially
4 valid, which says if you look at all of the
5 different components of the four major measures,
6 the different components don't necessarily have
7 overlap.

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

19 I would have loved to see also a mediator
20 analysis on whether the changes in plaque explain
21 much of the differences in the cognitive endpoints,
22 which is of course the burden of proof. The burden

1 of proof is we targeted the oligomers of the
2 amyloid hoping that that would have an impact
3 clinically, and our question is does that bear up;
4 if it's a strong enough effect? I must say I care
5 more about the clinical aspects than I do about
6 the --

7 DR. FOUNTAIN: Right.

8 DR. EMERSON: -- pathology.

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

12 DR. FOUNTAIN: I think that's an excellent
13 summary of our discussion on this particular first
14 question, and that is, to be crude about it, none
15 of us like it, but if you force it to disregard
16 301, it appears that 302 could be positive and that
17 there is evidence of effectiveness. But this
18 subcomponent analyses, while they seem to support
19 it aren't necessarily overwhelming, is what I think
20 I understand the general discussion to be, with
21 thoughts among all the different details and
22 subcategories we talked about.

1 I'd just take my prerogative of one final
2 comment that there is a dose response, it appears,
3 in 302 for amyloid reduction based on the
4 information we were given. So I'm just agreeing
5 with your last point that there are some trends
6 towards that.

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

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

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

13 DR. PERLMUTTER: Joel Perlmutter.

14 DR. FOUNTAIN: Okay. Dr. Perlmutter?

15 DR. PERLMUTTER: I just want to make a
16 couple of points. First of all, I do think that
17 having this discussion point is being foist upon us
18 and is artificial. The specific points about 302,
19 I'm concerned about describing the benefits as
20 multiple endpoints when I do believe we saw data
21 that they are correlated; multiple endpoints are
22 correlated. I think we see a lack of correlation

1 between the A-beta change and the clinical endpoint
2 CDR-SB. I think that's a concern.

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

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

16 DR. FOUNTAIN: Okay. I think it's important
17 that we don't think anything is foist upon us. The
18 purpose of this discussion is to have the
19 discussion we're having that raised the concerns in
20 the relevant areas and not -- and you can disagree
21 or agree. And now we're about to vote on a very
22 specific --

1 DR. THAMBISETTY: Dr. Fountain, may
2 I -- Dr. Fountain, I have not had a chance to weigh
3 in on this question either, so I'm just
4 wondering --

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

7 Dr. Thambisetty?

8 DR. THAMBISETTY: Yes.

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

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

21 Are you suggesting that I expand upon why
22 I'm concerned right now or after we vote?

1 DR. FOUNTAIN: If you have additional
2 concerns we haven't discussed, then you can say
3 them right now.

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

15 What makes this especially concerning is
16 that the primary endpoint, which is the CDR sum of
17 box scores, is entirely dependent upon subjective
18 information that is provided to the rater by
19 patients and their caregivers, and the same goes
20 for the secondary endpoints like the NPI or the
21 ADCS-MCI scale. These scales are very, very
22 sensitive to biases due to expectations on the part

1 of patients and caregivers when they realize that
2 they're on the treatment arm which is very likely
3 to have occurred when you're being called in to
4 come in for additional MRI scans because you have a
5 drug-related adverse event.

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

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

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

20 DR. THAMBISETTY: Correct.

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

1 vote?

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

15 This is also present as a relative
16 difference of 22 percent from placebo. But what do
17 these changes mean in terms of their functional
18 significance? Do they represent tangible
19 real-world benefit? Are they clinically important?
20 This is what is captured by the concept of minimal
21 clinically important difference, and that's defined
22 as a smallest difference in score and the domain of

1 interest, which patients perceive as beneficial and
2 which would mandate in absence of any troublesome
3 side effects and cause a change in patient's
4 management.

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

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

18 DR. THAMBISETTY: That is correct.

19 DR. FOUNTAIN: I think we have the
20 opportunity now to ask the FDA a question about the
21 correlation of amyloid with clinical change in
22 Study 302. I'm not sure who's -- Dr. Dunn,

1 Dr. Krudys, or someone else is going to address
2 that.

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

12 Second, I think in terms of correlation, you
13 have to realize that the changes in the biomarkers
14 are changing over time and it's just a snapshot of
15 what we see at week 78. There could be a delay
16 between the change in the biomarker and the change
17 in the scale like CDR-SB, so that's not taken into
18 account. I know the sponsor has done some work
19 with the model that can describe the time course in
20 terms of the change in the reduction of brain
21 amyloid versus CDR-SB, and they did find a
22 relationship.

1 So those are few things I think the
2 committee should keep in mind in terms of thinking
3 about the correlation. And second, I'll just say
4 that it's not like change in beta-amyloid are being
5 used as a surrogate here. It's a biomarker of what
6 the drug is doing, and there is some correlation
7 between the changes and changes of clinical
8 outcomes.

9 DR. FOUNTAIN: Okay. Thank you.

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

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

20 DR. BONNER: For the record, LaToya Bonner,
21 questions 2, 4, 6, and 8 are voting questions.
22 Voting members will use the Adobe Connect platform

1 to submit their vote for this meeting. After the
2 chairperson has read the voting question into the
3 record and all questions and discussions regarding
4 the wording of the vote question are complete, the
5 chairperson will announce that voting will begin.

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

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

21 Next, the vote results will display on the
22 screen. I will read the vote results from the

1 screen into the record. Thereafter, the
2 chairperson will go down the roster and each voting
3 member will state their name and their vote into
4 the record. You can also state the reason why you
5 voted as you did if you choose. However, you
6 should also address any subparts of the voting
7 question if any.

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

10 (No response.)

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

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

18 Any clarification needed for the nature of
19 this question?

20 (No response.)

21 DR. FOUNTAIN: Okay. So if there are no
22 further concerns about the wording of the question,

1 we'll now begin the voting on question 2.

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

4 (Voting.)

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

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

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

16 DR. KESSELHEIM: This is Aaron Kesselheim.
17 I voted no. I think a lot of the reasons I voted
18 no were discussed in the discussion period, so I'm
19 not going to be able to go through all of them in
20 detail. But I think the fact that this was not a
21 full study, there is a suggestion of an effect but
22 there are enough red flags in terms of the changes

1 to the protocol, the concerns about unblinding, and
2 the observation of the effect in the 78-week
3 analysis. Without a full cohort of patients being
4 able to contribute to that analysis, to me doesn't
5 add up to a strong evidence.

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

16 Next is Dr. Duda.

17 DR. DUDA: I voted uncertain, which I guess
18 I would argue whether or not that would mean I'm
19 abstaining. I'm abstaining from committing either
20 way I guess. But I agree, I think it was a
21 positive study. It met its primary outcome even
22 though it was truncated early. I, however, still

1 have concerns that prohibit me from saying that
2 there's strong evidence.

3 DR. FOUNTAIN: Dr. Perlmutter?

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

18 DR. FOUNTAIN: Okay.

19 DR. BONNER: Excuse me. Hello?

20 DR. FOUNTAIN: Yes?

21 DR. BONNER: This is LaToya, DFO. I want to
22 restate the voting results for the record. So I

1 will restate the voting results: 1 yes; 8 nos; and
2 2 uncertain. I wanted to make that correction.

3 Thank you. You can proceed.

4 DR. FOUNTAIN: Thank you.

5 Next, Dr. Hoffmann?

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

14 DR. FOUNTAIN: Okay.

15 Dr. Kryscio?

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

18 DR. FOUNTAIN: Thank you.

19 Dr. Thambisetty?

20 DR. THAMBISETTY: I voted no mainly for the
21 reasons I specified earlier about dosing worsening
22 participants of the placebo arm, unblinding, and

1 the lack of appreciable minimal clinically
2 important difference. Thank you.

3 DR. BONNER: Thank you.

4 Dr. Alexander?

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

14 There were I think six or seven reasons I
15 voted no. The statistically significant effect was
16 limited to the high dose, I believe, not the low
17 dose. Forty percent of the ITT analysis didn't
18 have the opportunity to complete week 78. There
19 was no correlation with the biomarkers among the
20 high-risk group if I understood recent comments,
21 which is where the purported effect was
22 demonstrated. Only statistically significant

1 effects were at the final endpoint, not at the
2 earlier endpoints or earlier time points I should
3 say.

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

12 DR. FOUNTAIN: Thank you.

13 Dr. Onyike?

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

20 The one thing I would add is that in my
21 view, treatment effect is not just about achieving
22 a p-value. It's very much about the meaningfulness

1 of the effect size, and I think Dr. Thambisetty
2 spoke very eloquently about that. What I would add
3 to what he said is that the effect sizes as I see
4 them do not appear to lie outside of what you might
5 observe in the test-retest variability that you
6 might observe in ordinary clinical practice. Thank
7 you.

8 DR. FOUNTAIN: Thank you.

9 Next is Dr. Emerson.

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

18 I will say that if it were true, I did have
19 a tendency to extrapolate wildly at, say, a
20 25 percent decrease in progression, if you will and
21 might translate into a 33 percent increase in the
22 time to, although we never saw a responder analysis

1 or anything like that to help us differentiate
2 those things. So that also was something that just
3 meant that I couldn't say as much.

4 DR. FOUNTAIN: Okay. Thank you.

5 Dr. Jones?

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

13 DR. FOUNTAIN: Alright. Thank you.

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

22 I'd like to suggest that we accept the

1 wording of this and we just discuss the issue,
2 unless someone has a specific way they'd like to
3 get clarity on it.

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

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

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

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

20 So I understand that 103 was not designed to
21 allow for prespecified efficacy analyses. I also
22 was interested that the FDA's own biostatistical

1 reviewer noted that the efficacy analyses performed
2 loose statistical significance after excluding
3 individuals who were initiating concomitant
4 medications for treatment of Alzheimer's disease.

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

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

8 DR. ALEXANDER: -- and that of 302. I'm not
9 sure if that's exactly right, but apparently the
10 effect was tremendously larger. And contrary to
11 302, the effect was larger -- [inaudible].

12 DR. FOUNTAIN: I think we lost you again.

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

14 DR. FOUNTAIN: Now we can.

15 DR. ALEXANDER: Okay. So I was just
16 concluding by saying that all of those points, the
17 fact that it was not designed to allow for
18 prespecified efficacy analyses; that statistical
19 significance was lost after excluding those taking
20 concomitant Alzheimer's meds; that the effect was
21 20 times larger than 302; and that also contrary to
22 302, the effect was larger in non-carriers than

1 carriers, all of those gave me pause. Thank you.

2 DR. FOUNTAIN: Thank you.

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

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

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

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

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

22 DR. FOUNTAIN: Not exactly. So the question

1 is the statistical analysis done on 302, and in
2 some degree on 103, brought up a lot of concerns
3 about methods of analysis and so forth. And I
4 wonder if you would like to comment on, or further
5 comment on, the use of 302, for instance, without
6 regard to 301.

7 DR. ALEXANDER: Do you mean 103?

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

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

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

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

18 DR. KRUDYS: Sure. I could take the second,
19 the carriers versus non-carriers. The sample size
20 for the treatment arms were about 30 to 40, so
21 cutting into samples, subgroups, is going to be a
22 pretty small sample size. So I'm not sure they

1 could get much from a subgroup analysis of a trial
2 as small as Study 103 was, so I'm not sure going to
3 the subgroups.

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

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

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

16 DR. ALEXANDER: Thank you.

17 DR. FOUNTAIN: Okay. Thank you.

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

22 DR. GOLD: No, I'll stipulate to the wording

1 of the question; it's not a problem. I'd just like
2 to understand when the FDA talks about supportive
3 evidence of effectiveness, is the FDA thinking that
4 the effects on the CDR sum of boxes and mini-mental
5 state in 103 are supportive despite the fact that
6 it was not designed or powered for that?

7 In the same question that had been raised
8 before that, there were other outcome measures in
9 103, presumably some of them more sensitive to
10 changes in cognition that showed no effect. I'd
11 like to understand how the FDA sees effectiveness
12 in 103 when you have a kind of mixed sort of data.

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

16 DR. GOLD: Correct, particularly when the
17 103 study was not designed for efficacy, and B,
18 when there are signals from other outcome measures
19 that showed putatively more sensitive outcome
20 measures but showed no effect.

21 DR. FOUNTAIN: Would you just like to make
22 that as a statement for FDA to consider or would

1 you like to ask that as a direct question?

2 (Laughter.)

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

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

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

15 So that was the intent. It wasn't intended
16 to provide an artificial exclusion of any of the
17 data, but in the context of the arguments that are
18 made in the briefing book, to take it layer by
19 layer. And we were hoping to get some insight from
20 the committee, and I think we are, and we were
21 listening hard. We were hoping to get some
22 insight, kind of building up layer by layer in

1 terms of how these things go.

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

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

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

1 that.

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

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

18 So the reason that those particular outcomes
19 take on relevance potentially is if the argument
20 about 302 that's made becomes relevant to the
21 consideration of 103, because those are the
22 outcomes that the study share. So it's just

1 designed to try to address those layers, peel them
2 back a little bit individually before, as one of
3 the committee members noticed, getting down to the
4 bottom, and there's more integrated approach. So
5 that was the intent. It was to just look at these
6 relationships as cleanly as we could.

7 DR. GOLD: Thank you, Dr. Dunn.

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

12 I think Dr. Kesselheim is next.

13 DR. KESSELHEIM: Thank you. It's Dr. Aaron
14 Kesselheim. I share the concern raised by
15 Dr. Gold. I also wanted to raise the point that it
16 is challenging to ask us to identify supportive
17 evidence for a trial in 302 that's already of
18 questionable strength in a trial like 103 that was
19 not designed to provide supportive evidence but was
20 designed for evaluation of other things of which
21 the efficacy measurements were a supplementary or
22 secondary component of that analysis.

1 As a result, I think that's why you're
2 getting in 103 efficacy results that seem very
3 discordant from the efficacy results that you see
4 in 302, in addition to the fact that the efficacy
5 results are observed over the course of a 54-week
6 study, whereas in figure 5 of the FDA documents,
7 there doesn't appear to be any effect of the
8 high-dose group at 50 weeks of analysis.

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

14 Then also by the way, to skip over
15 301 -- because, again, the way that you try to
16 bolster a study like 302 is by looking at another
17 well-designed similar study, but that other study
18 which is 301, which, again, we're not supposed to
19 be talking about in this context of this question,
20 is a negative study. So for me, I think for those
21 reasons, Study 103 provides minimal support.

22 DR. DUNN: Thanks, Dr. Kesselheim. Can I

1 ask you to comment on the points that were made
2 about the relationship between the 0- to 54-week
3 dosing in 103 and the 26- to 78-week dosing in 302,
4 301 and 302? Can you tell me your thoughts about
5 that, please?

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

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

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

22 DR. DUNN: Okay. I'm sorry. Let me be a

1 little more direct. There were some points made in
2 the briefing book about the fact that the
3 equivalent time period to compare in 301 and 302 to
4 103 is the 26- to 78-week window. There's a
5 titration period involved in Studies 301 and 302,
6 and the briefing package made a point to say that
7 the relevant time period of comparison between
8 0 and 54 in 103 is 26 to 78 in 301 and 302 because
9 of the absence of titration in the 10-milligram
10 group in 103. I was just wondering if you had
11 noted that or had any thoughts about that.

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

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

20 DR. KESSELHEIM: Thank you.

21 DR. FOUNTAIN: Okay.

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

1 a comment.

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

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

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

20 I think I might like to ask the applicant to
21 comment on that. I don't have precise numbers at
22 my fingertips, but I believe the applicant has

1 informed us that, actually, they powered their
2 study for an effect size very similar to what they
3 observed. I might be wrong about that, and if I
4 am, I apologize. But could we have the applicant
5 comment on that, please?

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

10 DR. FOUNTAIN: Okay. Thank you.

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

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

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

20 DR. HAEBERLEIN: In the study that was
21 positive, the less data obviously makes it more
22 difficult to achieve that statistical significance,

1 but nonetheless you did still have statistical
2 significance. In the study that was not positive,
3 as you've seen in the briefing book, we've
4 understood what differentially impacted that study.

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

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

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

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

16 I'm having a lot of trouble with the details
17 because in the big picture, for instance 302 being
18 positive and being statistically significant, it's
19 a small difference and there's a lot of other
20 details. But fundamentally if you look at 103 in
21 its final analysis, there's statistical
22 significance that's seemingly meaningful at the

1 10-milligram per kilogram dose, and it's across
2 subgroups, and same for 302.

3 So I'm having trouble understanding why 302
4 should be so thoroughly rejected if it's positive.
5 I understand why 301 would be rejected, but I'm
6 having trouble understanding 302, and it seems to
7 be 103, because it looks in the same direction as
8 302 and would support 302. So I understand why
9 there's no question 301 is negative. That's not
10 even an issue. But it seems to me there's no
11 question 302 is positive and that 103 found a
12 difference at the 10-milligram per kilogram dose,
13 which would support it.

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

18 DR. EMERSON: Yes. This is exactly the point
19 that I wanted to make. 103 was a preliminary
20 screening trial. Had it been completely negative,
21 301 and 302 would have never been done. Phase 2
22 studies are always positive in some way, and what's

1 nice about 103 in this particular case is I viewed
2 the modifications to the eligibility criteria and
3 what else they were doing as relatively slight.
4 There are other times where you're chasing after
5 subgroups and you're just saying it's there, but
6 every phase 2 study is so impossibly biased in its
7 treatment effect that you should never be surprised
8 when you get less result in the confirmatory study.

9 Because of that, I gained some solace from
10 103. The thing that bothered me the most is,
11 again, due to pressures of time -- and, again, this
12 is a direct complaint -- and so much time spent
13 telling me things were excessively understood and
14 very persuasive and not enough time looking at the
15 data, I never got to really delve into what the
16 problems were with the randomization schemes and
17 direct comparisons, and particularly direct
18 comparisons by randomization comparison
19 superimposed on the 302 results before I'd believe
20 it was very supportive.

21 So there is something to be gained. If you
22 told me you had 302 with no phase 2 study, I'd say,

1 "Great. Give me two more confirmatory studies,"
2 but in no sense would I regard that 103 is going to
3 be the place of another confirmatory study. That
4 doesn't make me relax criteria for what would
5 regard 302 as pivotal. And just note that an
6 underpowered study decreases the positive
7 predictive value of a positive result. Lots of
8 people go, "Well, yeah, it was a small study but
9 the effect was huge." Well, they've got cause and
10 effect wrong.

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

18 So the positive predictive value, we don't
19 just want to worry about the type 1 error which
20 says make certain we don't approve distilled water
21 and the sponsor wants to say if we have an
22 effective drug, it really works. That's the power.

1 But we are concerned with the Bayesian positive
2 predictive value, and in an underpowered study, and
3 one in which you let the type 1 error creep up,
4 it's very low.

5 This is the reason why confirmatory studies,
6 depending upon the diseased area and depending upon
7 how much we know about it, anywhere between
8 20 percent and 70 percent of phase 3 studies
9 confirm the phase 2 results, and it has to do with
10 that positive predictive value.

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

16 DR. EMERSON: That was it.

17 DR. FOUNTAIN: Okay. Great.

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

21 DR. PERLMUTTER: I do. I just want to point
22 out that I would say 103 does not support 302, and

1 that is the high dose. 103 initially looked like
2 it was 0.04, but then after you exclude those who
3 had concomitant AD meds, it was 0.095. So there's
4 no direct support there.

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

10 DR. THAMBISETTY: Thank you, Dr. Fountain.

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

13 DR. THAMBISETTY: Yes, please.

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

1 directly from the Nature paper.

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

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

21 The other quick point that I'd like to make
22 is there also does not appear to be a strong

1 dose-response effect in Study 103. I can give you
2 one example. In tables 25 and 26 of the briefing
3 document, using an ANCOVA model, the magnitude of
4 change in MMSE scores in 3 milligram versus placebo
5 comparison is 1.7 MMSE points, and this is at a raw
6 unadjusted p-value of 0.07. This is more than
7 3-fold higher than in the 6-milligram per kilogram
8 comparison with placebo, which is with the raw
9 unadjusted p-value of 0.61.

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

17 DR. FOUNTAIN: Okay. I guess that's
18 reflected in the FDA slide presentation we saw
19 today on slide 33, which listed the outcomes by
20 dose, which look like a dose response. But what
21 you're saying is, first, that only the final
22 10-milligram per kilogram dose was statistically

1 significant at 0.04, and for the CDR sum of boxes
2 and for the MMSE, at 0.03. But you're saying if
3 that's corrected beyond the ANCOVA model that was
4 used here, that p numbers become even worse and not
5 significant. So you wouldn't think there is dose
6 response for clinical outcomes in 103.

7 Is that a summary?

8 DR. THAMBISETTY: Yes, and also the
9 3-milligram per kilogram dose seems to have a
10 warping effect on MMSE compared to the 6-milligram
11 per kilogram dose, which again goes against a
12 dose-response effect. So the 3-milligram per
13 kilogram dose --

14 DR. FOUNTAIN: Small --

15 (Crosstalk.)

16 DR. FOUNTAIN: Right. Okay.

17 So maybe we should move to vote 4. It looks
18 like we've addressed this, and everyone's questions
19 have been answered, and we seem to have a lot of
20 consensus discussion on this. So let's move to
21 number 4. Does Study 103 provide supportive
22 evidence of the effectiveness of aducanumab for the

1 treatment of Alzheimer's disease? Yes, no, or
2 uncertain.

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

5 DR. FOUNTAIN: Sure.

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

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

20 DR. FOUNTAIN: I think we're asked the
21 question here. I think we'll have to ask Dr. Dunn
22 to elaborate on that, but I understood Dr. Dunn to

1 say that in their briefing materials, they
2 presented this discussion and they wanted us to
3 address it. So one of the supportive lines of
4 evidence for the effectiveness of aducanumab could
5 come from 103, and they're asking us if we think
6 that's true or not or uncertain. And I guess it'd
7 be no if it was ineffective.

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

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

1 as primary evidence and presents 103 as supportive
2 evidence.

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

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

20 When you say does it provide evidence of
21 ineffectiveness, what does that look like to you?
22 What would that look like to you conceptually?

1 DR. ALEXANDER: Hi. This is Caleb
2 Alexander. We just had a lengthy discussion about
3 the various reasons for concern in using 103 to
4 support 302, and frankly I think a lot of those
5 will come out in the explanations of our answers to
6 this question. So again, I don't mean to provide
7 an unnecessary speed bump here.

8 DR. DUNN: No, no --

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

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

18 Let me just ask one clarifying question,
19 which really should help me. Are you using
20 evidence of ineffectiveness synonymously with a
21 lack of evidence of effectiveness, like a complete
22 absence of that? Is that what you mean by that?

1 DR. ALEXANDER: No. No. I view evidence of
2 ineffectiveness as different from evidence of a
3 lack of effectiveness. Thank you.

4 DR. DUNN: Thank you.

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

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

21 If there are no more
22 comments -- Dr. Thambisetty, do you have another

1 comment about this or is your hand still raised
2 from last time maybe?

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

5 DR. FOUNTAIN: Okay.

6 So if we don't have any other comments or
7 questions, we can move to begin voting on question
8 4.

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

12 (Voting.)

13 DR. BONNER: For the record, the vote
14 results are displayed, zero yes, 7 nos,
15 4 uncertain. I will now turn the meeting back
16 over to the chair.

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

22 DR. KESSELHEIM: Thank you. This is

1 Dr. Kesselheim. I voted no. Following
2 Dr. Fountain's rubric, since I don't think that 302
3 provides solid evidence of the effectiveness of the
4 drug, it's challenging for me to also think that
5 Study 103 provides supportive evidence.

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

17 DR. FOUNTAIN: Okay. Dr. Onyike?

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

22 DR. FOUNTAIN: Dr. Duda?

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

6 DR. FOUNTAIN: Thank you.

7 Dr. Alexander?

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

19 Then the last two points that have been
20 pointed out, one, some highly sensitive measures
21 did not reach statistical significance. Then
22 finally, as was recently mentioned I think by

1 Dr. Thambisetty, there was a lack of a strong
2 dose-response relationship.

3 DR. FOUNTAIN: Thank you.

4 Dr. Hoffmann?

5 DR. HOFFMANN: I voted uncertain because of
6 some of the same reasons everybody else has. It
7 asked is it supportive of a given study and yet we
8 don't know what study to use. We can't really view
9 302 in isolation. This was a phase 2 exploratory
10 study. It was much smaller. It only used two
11 efficacy scales versus six as in the other larger
12 studies. And for all of those reasons, I voted
13 uncertain. Thank you.

14 DR. FOUNTAIN: Thank you.

15 Dr. Kryscio?

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

18 DR. FOUNTAIN: Dr. Thambisetty?

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

1 endpoints. Thank you.

2 DR. FOUNTAIN: Thank you.

3 Dr. Perlmutter?

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

6 DR. FOUNTAIN: Thank you.

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

15 Dr. Emerson?

16 DR. EMERSON: This is Scott Emerson. I
17 voted no. On Study 103, the positivity or any
18 evidence it has is a prerequisite for the other
19 clinical trials but just for added emphasis. In no
20 way would I be accepting regarding this as an
21 adequate and well-controlled trial to make it two
22 there. We need confirmatory studies. So again,

1 302 as a pivotal study or 302 and 301 as two
2 confirmatory studies are there, but 103 cannot take
3 the place of another confirmatory study.

4 DR. FOUNTAIN: Dr. Jones?

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

12 DR. FOUNTAIN: Thank you.

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

20 In my mind that's a little bit of a two-part
21 question. First is what you think of all those
22 markers and how they were assessed, and second,

1 what is the significance of those markers? You
2 might interpret it differently. That's how I would
3 interpret that question.

4 First, let's open it up for other
5 interpretations or questions on the wording.

6 Dr. Hoffmann, you may have your hand up from
7 last time.

8 DR. HOFFMANN: Not really on the wording,
9 but on the concept. I think aducanumab did show a
10 demonstrable effect on amyloid, hopefully, the
11 exact species, which we don't know which is the
12 toxic species yet and could be one concern.

13 Also, in a smaller number, people were shown
14 to reduce tau as a downstream indicator, but in
15 several studies that I've reviewed, in fact
16 recently in JAMA Neurology, in June there was an
17 extensive study out of the University of Kentucky
18 Alzheimer's disease department that showed over
19 69 percent of the patients who died of dementia.
20 In their autopsies it showed multiple
21 proteinopathies, including beta-amyloid and tau,
22 but also alpha-synuclein and another DNA-related

1 drug. I think it's called TDP-43.

2 I think one of the problems we have with all
3 these neurodegenerative agents is we'll target one
4 or two of the epitopes that we're looking at to
5 modulate the neuron loss, but we don't really know
6 all of the proteinopathies that are taking place
7 until the person dies. So even in this study, I
8 believe a big portion of those discordant results
9 could have been mixed pathologies that we're
10 totally unaware of in the patient groups between
11 301 and 302, so I think we should take that into
12 consideration. We just don't know. It may have a
13 good effect on amyloid beta and tau, but what about
14 all these other misfolded proteins that could be
15 present that we won't know and we can't identify
16 now at least until autopsy?

17 DR. FOUNTAIN: Okay.

18 Dr. Thambisetty?

19 DR. THAMBISETTY: Thanks, Dr. Fountain.

20 I think from the results published from 103
21 as well as with 301 and 302, there's clear evidence
22 from brain amyloid PET imaging that aducanumab dose

1 dependently clears amyloid plaque from the brain.
2 I think that's pretty compelling. The drug appears
3 to generate precisely the neuroimaging biomarker
4 that you would expect by virtue of target
5 engagement. I don't think there's any doubt about
6 that in my mind.

7 But in the larger context of the discussion
8 today, particularly with relevance to the impact of
9 aducanumab and slowing some of disease progression,
10 the question is whether lowering of brain amyloid
11 burden as evidenced by PET imaging results in a
12 clinical benefit. I think those are very distinct
13 questions, but I think one follows the other very
14 logically.

15 With regard to this question, I think the
16 data are far less compelling. I would point to
17 slide 20 of the FDA statistical reviewer's
18 presentation, where you examine the relationship
19 between change in global brain amyloid burden at
20 week 78 in individuals exposed to high-dose
21 aducanumab and change in the CDR sum of box scores.
22 There really appears to be no relationship either

1 in Study 302 or 301, and this appears to be the
2 case even when the analysis is restricted to only
3 individuals exposed to the 10-mg per kilogram dose.

4 I think there are some larger implications
5 of these findings which we are not tasked with
6 discussing today. One of the larger questions
7 relevant to these observations is whether lowering
8 brain amyloid burden is in fact the correct target
9 in Alzheimer's disease, but like I said, I think
10 that's beyond the remit of the discussion today.
11 Thank you.

12 DR. FOUNTAIN: Okay.

13 So it looks like we're going to be
14 relatively short on time, so in this question in
15 particular we might be able to group our answers.
16 Let's see if we can try to consolidate them a bit.

17 I think next up is Dr. Duda.

18 DR. DUDA: I in that vein agreed that I
19 think the evidence is fairly compelling that
20 there's an effect on AB in the brain. A number of
21 us are having difficulty with the lack of an
22 association between the CDR-SB and the PET imaging.

1 I think it would be very helpful if the
2 statistician and the other members of the FDA team
3 had come together and tried to understand the
4 discrepancy between the two analyses. If it really
5 was just a ceiling effect or a power problem, why
6 was one analysis suggesting a correlation and
7 another not? I think that directly impacts on how
8 I feel about the impact of that finding.

9 DR. FOUNTAIN: Okay. That's understandable.
10 Dr. Gold?

11 DR. GOLD: Hi. I just wanted to say that at
12 least one of the things that we got excited about
13 when we saw the 103 study when it first came out
14 was there was unequivocal evidence of target
15 engagement, so this was remarkably positive data.
16 It was clear that there's a dose proportional
17 response. In some of that we see both.

18 I'm looking at the clinical reviewer's
19 graphs in the briefing document. That's been
20 replicated in the study, albeit in subgroups.
21 Where I'm having more issues in terms of the actual
22 downstream biomarkers is the effect actually on tau

1 because that's really what we believe drives the
2 neurodegeneration.

3 So the effect on tau are not quite as clear,
4 partially because it's tiny sample sizes. And I
5 understand that subjects in studies may not like to
6 have lumbar punctures, so that limits the amount of
7 data that we can collect.

8 The part that I'm struggling with also is
9 when we actually look at the effect on tau using
10 PET, that although there's an effect in reducing
11 tau, the vast majority of the data on tau effect
12 comes from the 301 study. So 31 out of 37 subjects
13 come out of the 301 study and presumably that's
14 where you're seeing downstream effects on tau. So
15 it appears that there's an effect on the downstream
16 biomarker, but if you believe it, it's just
17 disconnected from a clinical effect.

18 DR. FOUNTAIN: Okay. Yes, I think that's
19 been mentioned before as well.

20 Let's take one more comment and then vote,
21 because in the vote also we have an opportunity to
22 state it. And I think Dr. Kesselheim is next.

1 DR. KESSELHEIM: This is Dr. Kesselheim. I
2 don't want to take too long. I just wanted to
3 applaud, in a sense, Biogen and the FDA here for
4 not simply resting on the effect of this drug on
5 the biomarkers because the effect of the biomarker
6 does seem pretty significant, but then actually
7 going on and doing the tests necessary to evaluate
8 the clinical effects of the drug and leading to the
9 discussion that we're having today.

10 Other than that, I think that what
11 Dr. Thambisetty and Dr. Gold said about those
12 biomarkers is right. We need to make sure that if
13 we are going to rely on biomarkers, that they are
14 well validated with their clinical endpoints.

15 DR. FOUNTAIN: Yes, I'd agree with that as
16 well, for my two cents.

17 I think we could probably move to the voting
18 now, and that will also give everyone an
19 opportunity to comment on this.

20 DR. PERLMUTTER: I'd like to comment. Can I
21 make a comment? This is Joel Perlmutter.

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

1 DR. PERLMUTTER: Joel Perlmutter.

2 DR. FOUNTAIN: Okay. If you have a brief
3 comment, that'd be great.

4 DR. PERLMUTTER: Yes. I'm kind of a world
5 expert on PET imaging.

6 DR. FOUNTAIN: Right.

7 DR. PERLMUTTER: So I'd think it would be
8 relevant.

9 I think, first of all, the comments about
10 the relationship of target engagement I think is
11 totally appropriate, but the disconnect or the lack
12 of correlation with the clinical benefit is a real
13 problem.

14 The second thing, that tau imaging was done
15 on a non-randomized group and we have also a huge
16 issue of off-target binding with the tau imaging
17 agent. So I don't think that really provides us
18 any specific information in this particular case.
19 I think the idea of going after these is terrific
20 and trying to find target is great, but whether
21 that's the right target or not, that's a bigger
22 issue that came up earlier, and I agree that's a

1 major problem. Thank you.

2 DR. FOUNTAIN: Okay.

3 Let's move to the voting, and of course
4 you'll have an opportunity during the voting to
5 discuss this as well.

6 DR. BONNER: Dr. Fountain, can we summarize
7 the discussion for question 5 please before we
8 proceed forward?

9 DR. FOUNTAIN: Yes. So the discussion is
10 that it seems as though there's evaluation of
11 several of the biomarkers listed here, and while
12 there's some evidence that they trend in the right
13 direction, because they don't co-trend entirely, or
14 sometimes at all, with the clinical outcome,
15 there's some concern about their value in
16 supporting it. But I think the overall impression
17 is that it supports some of the pathological
18 hallmarks of Alzheimer's disease, but there's a lot
19 of individual considerations for each of the
20 biomarkers with variable opinions about the degree
21 of confidence.

22 Okay. So now we can move to the voting

1 question, which parallels the discussion question.
2 Has the applicant presented strong evidence of a
3 pharmacodynamic effect on Alzheimer's disease
4 pathology? Yes, no, or uncertain. Any discussion
5 on the wording before moving to the vote?

6 DR. THAMBISETTY: I have one comment on the
7 wording.

8 DR. FOUNTAIN: Just before you begin, if we
9 could have everyone raise your hand if you have a
10 comment on the wording; otherwise, you could maybe
11 look and make sure your hand is unraised.

12 Was that Dr. Thambisetty?

13 DR. THAMBISETTY: Yes, Dr. Fountain, if I
14 may?

15 DR. FOUNTAIN: Yes.

16 DR. THAMBISETTY: I want to clarify whether
17 or not this question includes effects of the
18 biomarkers related to brain pathology as well as
19 reading out clinical effectiveness because those
20 are two completely different questions. I want to
21 be sure I understand that the question is capturing
22 one or the other, or both in this.

1 DR. FOUNTAIN: I think understand the
2 question, and I think we can ask the FDA if we're
3 undecided, but I think we get to decide that. And
4 I think the question crosses anything you think
5 might be pharmacodynamic mostly related to what I
6 would call biomarkers that we talked about in the
7 discussion.

8 DR. THAMBISETTY: If I think that there's
9 good biomarker evidence for brain pathology but not
10 good biomarker evidence for clinical efficacy, how
11 would I vote on this question?

12 DR. FOUNTAIN: You'll have to decide for
13 yourself if that constitutes strong evidence of a
14 pharmacodynamic effect on Alzheimer's disease
15 pathophysiology.

16 DR. THAMBISETTY: Got you. So you think the
17 term "pathophysiology" would also include treatment
18 effects and therapeutic efficacy?

19 DR. DUNN: Dr. Fountain, you may
20 intentionally be not wanting me to clarify --

21 DR. FOUNTAIN: No --

22 DR. DUNN: -- in order to --

1 (Crosstalk.)

2 DR. FOUNTAIN: -- that would be great if
3 you'd clarify.

4 DR. DUNN: Okay. It's always interesting to
5 work on questions hard and then see how people read
6 them. This question was absolutely intended to
7 represent the biomarker-based assessment of the
8 pathology of Alzheimer's. Really, we're talking
9 about amyloid and tau, and there was also obviously
10 some downstream effects, not specifically. But
11 that's what we're talking about here, mainly
12 amyloid. But it's not a clinical meaningful
13 question. It's about what effect has been
14 demonstrated using the biomarkers that we have on
15 the pathophysiological findings.

16 DR. THAMBISETTY: Got you. So no relation
17 whatsoever to clinical effectiveness and the
18 biomarker profile.

19 DR. DUNN: Yes. I'm wondering maybe if the
20 word "strong" is what's got you thinking that.

21 DR. THAMBISETTY: Exactly. Exactly.

22 DR. DUNN: Yes. That's really meant to

1 speak to the evidence on the marker itself. So you
2 can probably pretty easily envision a marker that
3 has -- in the abstract, a random drug might have
4 some of what you might think of as weak evidence on
5 a marker, and this is really meant to get at the
6 type of thing that Dr. Gold was commenting on
7 before, and I think you were as well.

8 DR. THAMBISETTY: Great, because we know
9 that PET imaging of amyloid does in fact measure
10 amyloid, but that's not the question that we're
11 being asked.

12 DR. DUNN: Yes. We're --

13 DR. ALEXANDER: I'm sorry. This is Caleb
14 Alexander.

15 Dr. Dunn, is another way of asking this
16 simply asking has the applicant presented strong
17 evidence that the product modifies biomarker
18 parameters of Alzheimer's disease, such as amyloid
19 plaques, and tangles, and tau, and stuff like that?

20 DR. DUNN: I think for the purposes that
21 you're asking it, Dr. Alexander, that's probably
22 okay, yes. That's not how I would word, but yes, I

1 think that's --

2 DR. ALEXANDER: I know that was a bit
3 verbose or not so eloquent, but the bottom line is
4 you're getting at whether we believe that the
5 product does or does not -- is there strong
6 evidence that the product has an effect on these
7 pathophysiologic measures of Alzheimer's disease.

8 DR. DUNN: That's right.

9 DR. FOUNTAIN: Okay. So that clarifies it I
10 think as much as we can.

11 Dr. Kryscio, I see you put your hand down.
12 I don't know if you still have a question.

13 DR. KRYSCIO: No. I'll cover it in the
14 comments on my vote.

15 DR. FOUNTAIN: Okay. So I think we can move
16 to the vote then.

17 DR. BONNER: For the record, LaToya Bonner.
18 We will now move voting members to the voting
19 breakout room to vote only. There will be no
20 discussions in the breakout room.

21 (Voting.)

22 DR. BONNER: LaToya Bonner. For the record,

1 results displayed for vote question 6, 7 yeses; 6
2 uncertain; zero nos.

3 I will now turn the meeting over to the
4 chair.

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

10 DR. KESSELHEIM: Thanks. This is
11 Dr. Kesselheim. I'm not sure why I keep going
12 first. Maybe it's the two A's in my first name.
13 But I voted uncertain because while it is very
14 clear that the drug provides substantial impact on
15 the biomarkers that it measured, because the effect
16 of the changes in those biomarkers on the clinical
17 impact of the drug is unclear, that left me
18 uncertain as to whether or not it had an impact on
19 Alzheimer's disease pathophysiology. Thank you.

20 DR. FOUNTAIN: Thank you.

21 DR. Onyike?

22 DR. ONYIKE: Yes. This is Chiadi Onyike. I

1 voted yes. I viewed the question narrowly. This
2 is a treatment designed to basically
3 [indiscernible] out amyloid pathology, so I view
4 the question as did it actually do that. There's
5 clear evidence that it did that in a dose-related
6 fashion.

7 There is some ambiguity, as Dr. Gold and
8 perhaps others discussed, regarding downstream
9 effects on tau, but fundamentally this compound is
10 not designed, at least in the pharmacodynamic
11 sense, to alter tau pathology -- to engage with tau
12 pathology. It's specifically designed to directly
13 engage with amyloid pathology, and it did that.
14 Thank you.

15 DR. FOUNTAIN: Thank you.

16 Dr. Duda?

17 DR. DUDA: This is John Duda. I voted yes
18 because I do believe there's strong evidence of a
19 pharmacodynamic effect on Alzheimer disease
20 pathology, specifically amyloid pathology, and in
21 my mind that justified a yes. Thanks.

22 DR. FOUNTAIN: Thank you.

1 Dr. Hoffmann?

2 DR. HOFFMANN: Yes. I voted yes, but
3 primarily because it was mentioned that we were
4 just talking about amyloid beta and tau. But again
5 I'd like to point out that I think there are a
6 number of other proteins that are misfolded that
7 could be involved in Alzheimer's that we really
8 don't understand yet. I think that's the reason
9 why you didn't see super excellent results with
10 this drug because if it was targeting all the toxic
11 species, I think we would have seen much better
12 efficacy results. Thank you.

13 DR. FOUNTAIN: Thank you.

14 Dr. Jones?

15 DR. JONES: Yes. This is Dawndra Jones. I
16 voted yes because I believed it clearly
17 demonstrated positive impact on the biomarkers,
18 especially concerning the amyloid pathology. Thank
19 you.

20 DR. FOUNTAIN: Dr. Perlmutter?

21 DR. PERLMUTTER: Well, I said uncertain, and
22 I agree with everybody actually. I think there's

1 no question it demonstrates engagement with the
2 A-beta amyloid. I think the tau is very uncertain.
3 The question in my mind is whether that's the
4 correct biomarker to use for the relevant clinical
5 effect.

6 DR. FOUNTAIN: Thank you.

7 Dr. Alexander?

8 DR. ALEXANDER: I voted uncertain. I just
9 want to say as an aside, because it's the last time
10 that I may speak, both to thank sponsors and the
11 FDA for the enormous amount of work that you put
12 into making today possible. I also want to just
13 note that the briefing packet was unique in that it
14 was co-produced, and I do think there's some merit
15 in having separate packets produced by both
16 parties, or at a minimum having the FDA provide the
17 briefing materials and having the sponsor add their
18 commentary to the FDA's review rather than vice
19 versa, given the FDA's role as regulator here.

20 Regarding this question at hand, I think it
21 is, as was noted, important to note that the
22 absence of correlation between the reduction in

1 amyloid and clinical efficacy, at least among the
2 high-dose group, I do think there's very good
3 evidence that the product reduces amyloid. But as
4 was noted, the impact on tau was more difficult to
5 understand the meaning of that because it was among
6 what I understand to be a selected or non-random
7 subset. Thank you.

8 DR. FOUNTAIN: Thank you.

9 Dr. Emerson?

10 DR. EMERSON: I tended to answer this
11 narrowly as did Dr. Onyike. The pathophysiology of
12 Alzheimer's include signs of amyloid deposits. I
13 think this has affected that. Whether it has
14 affected symptoms or clinical sequelae that matter
15 more is unclear, but in the sense that something
16 has changed, I said yes.

17 DR. FOUNTAIN: Thank you.

18 Dr. Thambisetty?

19 DR. THAMBISETTY: I voted uncertain because
20 while I think the biomarker profile in terms of
21 amyloid is very elegant and compelling, it becomes
22 a little bit murky in terms of tau, so I think the

1 sample size is rather small. There's considerable
2 heterogeneity in baseline power levels that we know
3 from previous studies, and tau PET, again, is a
4 fairly novel imaging modality that hasn't been
5 fully validated in very large cohorts. So for
6 those reasons, I voted uncertain.

7 DR. FOUNTAIN: I'm next, Nathan Fountain. I
8 voted uncertain because I think there is evidence.
9 I'm not sure how strong it is, though, but I do
10 think there's evidence.

11 Next is Dr. Kryscio.

12 DR. KRYSCIO: Yes. I voted uncertain
13 because I guess I'm at a neuropathology center, and
14 it's not a hundred percent clear what's measured by
15 PET; it's actually what is measured at autopsy. Of
16 course I agree that the evidence for tau is very
17 low here.

18 I'd also like to add, because it was
19 discussed before, the other proteinopathies, which
20 is TDP-43 and alpha-synuclein. I don't know if
21 they're really issues in this particular case.
22 They certainly could contribute to the reasons why

1 people get a clinical diagnosis of dementia, but
2 that usually occurs when you're over 80, and the
3 people in this study were in their 70s. So I'm not
4 so sure that plays a big role in this particular
5 case.

6 DR. FOUNTAIN: Thank you.

7 Alright. We'll now move on to number 7,
8 which is a discussion question.

9 Study 301 was a negative study. Post hoc
10 exploratory analyses were conducted in order to
11 achieve maximum understanding of the partially
12 discordant results of Studies 301 and Study 30, and
13 to determine if this understanding precludes
14 independent consideration of Study 302.

15 Additional contribution to the understanding
16 of aducanumab's pharmacological activity and
17 clinical effects is provided by the results of
18 Study 103. In light of the exploratory analyses
19 that were conducted and the results of Study 103,
20 discuss the impact of the results of Study 301 on
21 the consideration of the results of Study 302.

22 If I might start the discussion by saying

1 we've pretty thoroughly said that -- maybe not all
2 of us, but there's a group. Our discussion before
3 was that Study 301 being negative makes it
4 difficult to interpret Study 302 for all the
5 statistical reasons considered before. But if
6 you'll raise your hands, we can have discussion on
7 this question now.

8 Dr. Emerson?

9 DR. EMERSON: Thank you. I'll just make
10 three points in addition to what's there. The
11 linear dose response, which much was made of that
12 being one of Koch's postulates and things you want
13 to do, none of this removed the fact that we did
14 not have a linear dose response in 301 with no
15 explanation of why it was there.

16 I'll note that I was very disturbed by some
17 of the FDA's interpretation of 301 by starting out
18 with the assumption that the treatment works, and
19 now trying to assay why do we get no results in
20 301. Usually we start off saying the treatment
21 doesn't work and are these compatible with it. And
22 I spoke to this earlier about if you assume the

1 treatment doesn't work, then it's not that rare to
2 have some strong results on one of the trials and
3 just completely nothing results. And that's
4 happened to me many times in my life when I've
5 monitored trials of the same.

6 Then lastly, I was very, very, very
7 disturbed by some of the analyses that were
8 considered. I was glad to hear Dr. Dunn soften
9 what they were doing and try to make clear. But I
10 will just state that some 20 years ago I was
11 involved as an expert witness in a scientific
12 misconduct trial of, as it turns out, an
13 Alzheimer's disease researcher who was removing
14 beta that she didn't like and just seeing what
15 happens, and that's just never acceptable to do.

16 So for the most part, the sensitivity
17 analyses were sometimes just completely
18 unnecessary. They were just reproducing the
19 statistics we already had. I'd like to say that if
20 you give me a study with a thousand subjects, I
21 view that as a thousand subjects and I'm missing
22 data on 7 billion others. And if you impute the

1 data on the 7 billion others, well, that's what we
2 already do with statistics, and that's what it
3 answers.

4 Then some of the other times, the missing
5 data -- I believe it was Dr. Alexander who said
6 earlier. But somebody said that the missing data
7 analyses were not very comprehensive to the
8 possibility of missing not at random, so I was
9 bothered with that. So I'll just leave it at that.

10 DR. FOUNTAIN: Okay. Thank you.

11 Next is Dr. Gold.

12 DR. GOLD: Just a quick comment. I think I
13 previously mentioned what I was struggling with is
14 the notion that it was almost passively accepted
15 that 302 represented truth and that 301 did not,
16 and it's a lot of effort trying to discredit or to
17 minimize the 301 data, so outlier analysis and
18 rapid progressors.

19 But all those things are generally taken
20 into account in the sample size estimates for the
21 study, so I just didn't understand why there seemed
22 to be this kind of unilateral effort to discredit

1 one study. It would have been interesting to take
2 the opposite position to say 301 represents truth
3 and what in 302 could have accounted for a false
4 positive signal, just to kind of have either the
5 falsifiable or counterfactual debate. So I think
6 that's part of the issue in terms of how 301
7 influences 302.

8 The other part is, if you think about -- and
9 I'm going back to some of the data that was
10 presented earlier. Again, post-Amendment 4, the
11 actual number of subjects that are impacted by that
12 amendment in terms of dose escalation in the
13 high-dose ApoE4 is miniscule. It's a really,
14 really small number of subjects, and it's difficult
15 for me to understand how big of an effect those
16 subjects had in 302 to make the results as
17 numerically positive as they are.

18 So I think it goes back to that first
19 question. For me, it's difficult to divorce an
20 understanding of 302 without thinking -- and it's
21 kind of a Bayesian thing, prior information and
22 prior knowledge. So I think it colored my

1 understanding or at least my level of comfort in
2 the efforts to try to dismantle 301 and the lack of
3 efficacy there.

4 Again, this is a hugely important decision.
5 Many of us came into industry because we dealt with
6 Alzheimer's disease patients either personally or
7 professionally. So I just want to unequivocally
8 state that there is no lack of empathy and
9 understanding of the misery and pain that the
10 disease causes, but I think this is a hugely
11 important decision that has and can have
12 repercussions across clinical research enterprises
13 and industry in terms of how do we interpret these
14 kind of studies and what is the standard of
15 evidence.

16 So for me -- and I'll stop after this -- I
17 think it's important to be respectful of the fact
18 that 301 was well designed, well conducted, and
19 well executed. There's no evidence that it was
20 somehow defective in any way, shape, or form, and
21 it's hard to ignore that. Thank you.

22 DR. FOUNTAIN: Thank you.

1 Dr. Alexander?

2 DR. ALEXANDER: Thank you. I took my hand
3 down. Thank you very much.

4 DR. FOUNTAIN: Okay. Dr. Duda?

5 DR. DUDA: Thank you. This is John Duda. I
6 kind of agree with the prior speakers. I just want
7 to say though, I think that it is noteworthy, the
8 collaboration that developed between the FDA and
9 the sponsor. I think obviously the sponsor was in
10 a tough position. There were some decisions that
11 were made that ended up probably not being
12 beneficial to them. They had obviously put in a
13 lot of resources into this compound, as has the
14 field as a whole, and trying to find a way out of
15 this unfortunate situation I think was laudable. I
16 think more collaboration between the sponsors and
17 the FDA is something that I'd like to see in
18 future.

19 However, I think that perhaps in the
20 future -- I don't think you would have
21 gotten -- maybe you would have gotten people
22 disagreeing with you that 301 was negative, but

1 instead of taking the approach of trying to explain
2 that away, I guess a better approach might have
3 been just to say, "Okay. Can we agree that 302 is
4 positive?" If you had just gone down that route,
5 we might not be where we are today.

6 But I think, all in all, the main -- I think
7 several of us have said it already. Dr. Massie's
8 criticisms just were never addressed in the
9 clinical overview, and there seemed to be a
10 disconnect between different aspects of the FDA
11 reporting that are very difficult for us to draw
12 conclusions from. So in light of that, I think it
13 makes it much more difficult to get where the FDA
14 maybe thought we would go today. Thank you.

15 DR. FOUNTAIN: Okay. And the last comment
16 from Dr. Thambisetty.

17 DR. THAMBISETTY: Thank you, Dr. Fountain.

18 I think both 301 and 302 were well-designed
19 phase 3 clinical trials and they provided
20 discordant results. I don't think the post hoc
21 exploratory analyses presented provide
22 justification for discounting or overriding 301 and

1 considering 302 independently. Thank you.

2 DR. FOUNTAIN: Okay. Thank you.

3 Let's move to issue 8, which is a vote,
4 question 8.

5 DR. DUNN: Can I just ask some of the folks
6 who were commenting about how they feel about what
7 we thought was clear on page 226? There's only so
8 many pages we can write of the history of this.
9 It's a short sentence, but I'm just kind of
10 curious.

11 DR. ALEXANDER: Can you project it? This is
12 Caleb Alexander. Would it be possible to project
13 it? I don't know that I can find the materials
14 easily.

15 DR. DUNN: Well, I could just read it.

16 "Upon initial review, the one positive
17 study, Study 302, and the one negative study, 301,
18 were given equal weight and consideration." And I
19 suspect if you ask the applicant to weigh in, I
20 think they will relate to you probably the degree
21 to which 301 was given credence for a very long
22 time, and it was quite clear that either study

1 could represent in the abstract truth.

2 So I'm just curious about the comments
3 because we wouldn't want to have conveyed that, and
4 I'm wondering if that was missed or if it wasn't
5 understood in the way that we intended it. That's
6 kind of what I'm getting at. And I wouldn't mind
7 asking the applicant actually to weigh in on that
8 aspect because I don't think there was any sense of
9 the people that were working on this that it was
10 entered into with a belief in 302 a priori and a
11 desire to throw 301 away. I remember taking great
12 pains to make sure that wasn't the case.

13 Maybe I can ask the applicant to weigh in on
14 that and also if people could just clarify if we
15 didn't communicate well our stance there.

16 DR. HAEBERLEIN: Yes, thank you. That was
17 absolutely the case through our investigations,
18 that we treated both studies equally, and the
19 resulting output of those investigations are indeed
20 that Study 302 is robust and that Study 301 is a
21 negative study. So that's not lending different
22 weight to truth, but that those outcomes are

1 different. The nature of our investigations were
2 to understand why Study 301 was a negative study.

3 DR. ALEXANDER: Dr. Dunn, if you review the
4 briefing materials -- I'm trying to pull up
5 selective pieces of them and -- and this is Caleb
6 Alexander -- I can't do so quickly. But the
7 framing of the briefing materials were very
8 much -- at least I interpreted them as very much
9 emphasizing an interest in identifying whether or
10 not 301 could still provide sufficient evidence for
11 302 as a stand-alone pivotal study.

12 And the conclusion that was stated by the
13 FDA used the words that the applicant has provided,
14 "substantial evidence of effectiveness," and
15 referred to 302 as a robust and exceptionally
16 persuasive study. And I believe what you've heard
17 today, as well as what's been communicated through
18 the vote, is that -- I don't want to presumably
19 speak on behalf of the entire committee, but
20 certainly I do not feel that the evidence has been
21 presented to support that view from the FDA.

22 So throughout the briefing materials in

1 many, many places, the emphasis is not on using 302
2 to understand why 301 was negative and raising the
3 question that perhaps 302 is really a negative
4 study, too. It's all framed in one direction,
5 which is using 301 to support 302. Thank you.

6 DR. PERLMUTTER: This is Joel Perlmutter.
7 Just to make a comment about impression of how the
8 data was presented to us is to just go to the first
9 discussion point. The first discussion point
10 seemed very biased in the sense that, okay, now
11 consider 302 and ignore everything in 301. That
12 just seems that we were being pushed in one
13 direction or there was a bias in that one
14 direction. So that really sums up how I perceived
15 the presentations.

16 DR. EMERSON: This is Scott Emerson. If you
17 thought that I was being critical, you're
18 absolutely correct. On page 226, one of the lines
19 that I felt was bad was you start off in saying,
20 "if it's effective," then it follows that that's
21 reflective of the two effects and there are
22 patients in Study 301 who, based on certain

1 characteristics, should show response.

2 Okay. The flip side is -- and I, again,
3 didn't have time earlier, but I was going to ask
4 for the analysis in which you added into Study 302
5 the patients who weren't represented that were
6 rapid progressors perhaps owing to the drug itself,
7 and you never did that analysis. So you were not
8 at all symmetric and you certainly were not
9 starting off with saying could these results be
10 explained by a null effect in which case you'd say,
11 yeah; nothing was going on in 301 -- that's the
12 truth -- and in 302, why did we get aberrant
13 results?

14 So the truth is probably somewhere in
15 between about the way to do it, but there was just
16 no question that all of this was just terrifically
17 one-sided. And again, I'm highly critical of the
18 fact that the FDA presentation today was so heavily
19 weighted to just giving the same conclusions that
20 the sponsor did, and that there was not
21 presentation by the statistician who'd done a
22 careful analysis and made many points that I was

1 very glad to see that the committee read.

2 DR. FOUNTAIN: I guess those points were
3 clear. I guess in the briefing document the point
4 was that they were considered individual, and one's
5 positive and one's negative, and if it's positive,
6 move forward.

7 Dr. Dunn, do you want us to vote on question
8 number 8?

9 DR. DUNN: No, that's fine. I'm sorry. I
10 didn't mean to interrupt too much there. I just
11 wanted to make sure that we were communicating
12 clearly as we need to. Thank you.

13 DR. THAMBISETTY: Dr. Fountain, may I make a
14 very quick point?

15 DR. FOUNTAIN: Sure, briefly.

16 DR. THAMBISETTY: Very good. I just wanted
17 to note that the discordant ways in which we have
18 perceived this question I think is also very aptly
19 summarized in the discordance between the FDA's
20 clinical reviewer and the FDA's statistical
21 reviewer. I think to paraphrase Dr. Tristian
22 Massie, if you have two, and you take the best and

1 pretend like it's the only one, your estimate is
2 likely biased. But I think that discordance is
3 captured in the way the FDA's clinical review and
4 statistical review differ as well. Thank you.

5 DR. FOUNTAIN: To summarize our discussion
6 for this, all along we've said there's been no
7 presumption 301 was positive; it's clearly
8 negative. The general idea is that 302 is
9 difficult to consider positive in light of 301 and
10 that 103 had some evidence of pharmacodynamic
11 effect as we generally said, but that's not
12 necessarily supportive. As a parenthetical point,
13 that the difference between the statistical
14 analysis in Appendix 2 and the clinical reviewers
15 is difficult for us to address.

16 So maybe we could move to point 8, the vote.
17 In light of the understanding provided by the
18 exploratory analysis of Studies 301 and Study 302,
19 along with the results of Study 103 and evidence of
20 a pharmacodynamic effect in Alzheimer's disease
21 pathophysiology, is it reasonable to consider
22 Study 302 has primary evidence of effectiveness of

1 aducanumab for the treatment of Alzheimer's
2 disease? Yes, no, or uncertain.

3 We can discuss the nature of the question,
4 although I would say our last discussion was pretty
5 thorough.

6 Dr. Emerson, your hand is up. Do you have a
7 question about the wording of this one or is that
8 something else?

9 (No response.)

10 DR. FOUNTAIN: Okay. Thank you.

11 So now I think we can move to the vote.

12 DR. BONNER: We will now move voting numbers
13 to the voting breakout room to vote only. There
14 will be no discussions in the voting breakout room.
15 For the record, LaToya Bonner.

16 (Voting.)

17 DR. BONNER: LaToya Bonner. For the record,
18 the vote is now closed. We are tallying the
19 results. Once the vote results are displayed, I
20 will read the vote results into the record.

21 (Pause.)

22 DR. BONNER: LaToya Bonner, DFO. For vote

1 question 8, we have zero yeses, 10 nos, and
2 1 uncertain.

3 DR. FOUNTAIN: Thank you. We will now go
4 down the list and have everyone who voted state
5 their name and vote into the record. You may also
6 provide justification of your vote if you wish to.
7 We'll start again with Dr. Kesselheim.

8 DR. KESSELHEIM: Hi. Thank you. This is
9 Aaron Kesselheim. I voted no. First of all, I
10 also wanted to echo what others have said, to thank
11 the FDA, and the sponsor, and Dr. Massie in
12 particular, for their thorough reviews of the
13 material and very helpful presentations.

14 I voted no for reasons that were discussed
15 in the prior conversation that I also discussed
16 earlier in these remarks today, so I'm not sure I'm
17 going to go over all of it again. Dr. Dunn pointed
18 out in his comments at the beginning of the day
19 that the evidence presented today provides
20 suggestive evidence of positive effectiveness that
21 the drug may be clinically active or that it's
22 possible that the results are persuasive.

1 I think all of those things are true. I
2 don't think that the evidence in Study 302 provides
3 substantial evidence of efficacy of effectiveness
4 of this drug and the way that 301 was sliced and
5 diced to support that further justifies that. So
6 to the extent that this question is asking about
7 the substantial evidence of efficacy standard, I
8 don't think that meets the standard.

9 DR. FOUNTAIN: Thank you.

10 I'm next, Nathan Fountain. I voted
11 uncertain because I do believe that 302 is positive
12 and that 103 provides some additional evidence and
13 there's some evidence in the markers. But of
14 course 301 was clearly negative, and it's hard to
15 say 302 could provide primary evidence, but it
16 can't provide all the evidence or substantial
17 evidence in my mind because of 301 and all the
18 issues we discussed.

19 Dr. Duda?

20 DR. DUDA: This is John Duda. I voted no I
21 think for all the reasons we've discussed and still
22 the remaining questions I have regarding

1 Dr. Massie's analysis that I think is still not
2 completely addressed. Thank you.

3 DR. FOUNTAIN: Thank you.

4 Dr. Hoffmann?

5 DR. HOFFMANN: Richard Hoffmann. I voted no
6 also for many of the reasons that were noted. I
7 really don't think looking at Study 301 you can
8 transform that into a positive study using a
9 post hoc analysis, so I agree with the other
10 committee members. Thank you all very much, and I
11 also would like to thank the FDA and the sponsor
12 for all their efforts.

13 DR. FOUNTAIN: Thank you.

14 Dr. Kryscio?

15 DR. KRYSCIO: Yes. It's Richard Kryscio. I
16 voted no for the reasons already specified, and I
17 would like to as well join the chorus of thanking
18 both the Biogen company as well as the FDA for
19 great presentations and easy to read.

20 DR. FOUNTAIN: Thank you.

21 Dr. Perlmutter?

22 DR. PERLMUTTER: Yes. This is Joel

1 Perlmutter, and I voted no for all the reasons we
2 discussed. But I specifically want to thank the
3 sponsor for moving forward and implementing
4 biomarker imaging to demonstrate target engagement.
5 I think the problem is, over the years since they
6 began it, it's not clear if that's in fact the
7 right target. Thank you.

8 DR. FOUNTAIN: Thank you.

9 Dr. Alexander?

10 DR. ALEXANDER: This is Caleb Alexander. I
11 voted no for all the reasons that I've previously
12 specified, and thank you again to everyone involved
13 in making today possible.

14 DR. FOUNTAIN: Thank you.

15 Dr. Emerson?

16 DR. EMERSON: I voted no and the reason has
17 been stated. I'm going to answer a question that
18 wasn't asked but often is.

19 What additional study would I want to see?
20 I personally think that a randomized withdrawal of
21 just the planned dose, and I'm uncertain of how
22 long to treat them before you do the withdrawal.

1 But certainly one of the speakers in the public
2 hearing remarked that they felt that they could
3 tell quickly that they were not having the effect.
4 Of course, I never know how true that is, but if
5 that's true, a randomized withdrawal design would
6 not be as big a burden as would be some of the
7 others and recognizing that in support, it should
8 be done. I personally hope that this treatment
9 pans out.

10 DR. FOUNTAIN: Thank you.

11 Dr. Thambisetty?

12 DR. THAMBISETTY: I voted no as well for all
13 of the reasons discussed throughout the day, and
14 I'd also like to take the opportunity to thank both
15 the applicant and the FDA for the privilege of
16 reviewing this hugely important work. I'd also add
17 a special note of thanks to Dr. Tristian Massie for
18 a really thorough statistical analysis that was
19 very, very useful. Thank you.

20 DR. FOUNTAIN: Thank you.

21 Dr. Onyike?

22 DR. ONYIKE: Yes. This is Chiadi Onyike. I

1 voted no. I think the record speaks adequately to
2 the reasons why. I would like to also place on
3 record my thanks to the sponsor. This is a
4 substantive, multi-effort. These things are not
5 easy to put together. It takes a lot of
6 commitment, and as we all know, this is a very big
7 unmet need.

8 As well, I'd say my thanks to the people who
9 participated in this study, as well as to the
10 families and advocates who've testified today; and
11 to the FDA, and in particular to Dr. Tristian
12 Massie for his work; and to you, Dr. Fountain, for
13 shepherding us through the meeting today. Thank
14 you.

15 DR. FOUNTAIN: Thank you.

16 Dr. Jones?

17 DR. JONES: Yes. This is Dawndra Jones, and
18 I voted no. I think it's really hard to ignore
19 some of the things that we have identified through
20 Study 301 as well as many of the things we have
21 talked about today. But I, too, want to thank the
22 FDA and the applicant because this work is

1 critical, and it's critical and much needed for
2 those patients and families that do suffer from
3 Alzheimer's disease. So I am very hopeful that you
4 will continue in this work so that we can
5 definitely help the individuals that suffer from
6 Alzheimer's. Thank you.

7 DR. FOUNTAIN: Thank you.

8 It looks like we have a consensus of opinion
9 here about this question and mostly about all the
10 questions. But before we adjourn, are there any
11 last comments from the FDA?

12 DR. DUNN: No. Thank you for your time,
13 very much appreciated

14 **Adjournment**

15 DR. FOUNTAIN: Thank you.

16 I'd just like to echo everyone else's
17 appreciation to Biogen and the FDA, and all the FDA
18 staff for putting together this production and all
19 of you for working through with us. It's sort of
20 like launching a space ship here to keep all of
21 this straight. So I want to thank all of you,
22 particularly the committee members who did such a

1 thorough job of reviewing the information, and also
2 the public speakers who went to all the effort and
3 trouble and distress, understandably speaking.

4 Thank you, everyone. We will now adjourn
5 the meeting. Thank you.

6 (Whereupon, at 5:06 p.m., the meeting was
7 adjourned.)

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