

**Summary Minutes of the Peripheral and Central Nervous System Drugs
Advisory Committee Meeting
November 6, 2020**

The Peripheral and Central Nervous System Drugs Advisory Committee (PCNS) of the Food and Drug Administration, Center for Drug Evaluation and Research, met on November 6, 2020. The meeting presentations were heard, viewed, captioned, and recorded through an online teleconferencing platform. Prior to the meeting, the members and temporary voting members were provided the briefing materials and pre-recorded presentations from the FDA and Biogen, Inc. The meeting was called to order by Nathan B. Fountain, MD (Chairperson). The conflict of interest statement was read into the record by LaToya Bonner, PharmD (Acting Designated Federal Officer). There were approximately 2,378 people online. There were sixteen Open Public Hearing (OPH) presentations.

A verbatim transcript will be available, in most instances, at approximately ten to twelve weeks following the meeting date.

Agenda: The Committee discussed Biologics License Application (BLA) 761178 for aducanumab solution for intravenous infusion, submitted by Biogen Inc., for the treatment of Alzheimer's disease.

Attendance:

Peripheral and Central Nervous System Drugs Advisory Committee Members Present (Voting): G. Caleb Alexander, MD, MS; Nathan B. Fountain, MD (*Chairperson*); Dawndra Jones, DNP, RN, NEA-BC (*Consumer Representative*); Aaron S. Kesselheim, MD, JD, MPH; Richard J. Kryscio, PhD; Chiadi U. Onyike, MD, MHS; Joel S. Perlmutter, MD

Peripheral and Central Nervous System Drugs Advisory Committee Members Not Present (Voting): David S. Knopman, MD; Michelle M. Mielke, PhD

Peripheral and Central Nervous System Drugs Advisory Committee Member Present (Non-Voting): Michael Gold, MS, MD (*Industry Representative*)

Temporary Members (Voting): John Duda, MD; Scott Emerson, MD, PhD; Richard P. Hoffmann, PharmD (*Patient Representative*); Madhav Thambisetty, MD, PhD

FDA Participants (Non-Voting): Eric Bastings, MD; Teresa Buracchio, MD; Billy Dunn, MD; Sally Jo Yasuda, PharmD

Acting Designated Federal Officer (Non-Voting): LaToya Bonner, PharmD

Open Public Hearing Speakers: Jeff Borghoff (The Alzheimer's Association in Greater New Jersey Chapter); Michael Carome, MD (Public Citizen); Geri and James Taylor; Kim and Kevin Bonham; Joanne Pike, DrPH (The Alzheimer's Association); Diana Zuckerman, MD (National Center for Health Research); George Vradenburg (UsAgainstAlzheimers); Meryl Comer; Greg O'Brein; Stephen Salloway, MD, MS; Peter Bristol; Edward Patterson;

John Dwyer (The Global Alzheimer's Platform Foundation); Pam Montana; Judge Nelson
Keith Brooks; C. Grace Whiting, JD (National Alliance for Caregiving)

The agenda was as follows:

Call to Order	Nathan B. Fountain, MD Chairperson, PCNS
Introduction of Committee and Conflict of Interest Statement	LaToya Bonner, PharmD Acting Designated Federal Officer, PCNS
FDA Opening Remarks	Billy Dunn, MD Director Office of Neuroscience Office of New Drugs, CDER, FDA
APPLICANT PRESENTATION	Biogen Inc.
Opening Remarks	Samantha Budd Haerberlein, PhD Senior Vice President Head of Neurodegeneration Development Unit Biogen Inc.
Clarifying Questions to Applicant	
FDA PRESENTATION	
FDA Summary Presentation	Billy Dunn, MD
Clarifying Questions to FDA	
LUNCH	
OPEN PUBLIC HEARING	
Questions to the Committee/Committee Discussion	
ADJOURNMENT	

Questions to the Committee:

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

Committee Discussion: *Some Committee members found it challenging to view Study 302 independently without regard for Study 301. Most Committee members noted that Study 302 could not be viewed without consideration of Study 301 since Study 301 was designed to be identical to 302 but was negative. Thus, few conclusions were drawn by the Committee members about Study 302. However, it was noted that the strength of Study 302 results was decreased because it was terminated before planned completion. There was discussion about whether 302 demonstrated clinical benefit despite the positive nature. The Committee recognized inconsistencies in the FDA data analysis from the clinical review and the statistical review, with many members endorsing the statistical review. Therefore, the Committee could not support the primary evidence of effectiveness provided by Study 302 of aducanumab for the treatment of Alzheimer's disease (AD), independently without regard for Study 301. Please see the transcript for details of the Committee's discussion.*

2. **VOTE:** Does Study 302, viewed independently and without regard for Study 301, provide strong evidence that supports the effectiveness of aducanumab for the treatment of Alzheimer's disease? YES/NO/UNCERTAIN

Vote Results: Yes: 1 No: 8 Uncertain: 2

Committee Discussion: *A majority of the committee members voted "No", that Study 302 viewed independently and without regard to Study 301 did not provide strong evidence that supports the effectiveness of aducanumab for the treatment of Alzheimer's disease. These members expressed the challenges in viewing Study 302 independently as a positive study without acknowledging the negative results rendered by a parallel study (Study 301). The members who were uncertain about the evidence noted that they could not view Study 302 in isolation knowing the existence of Study 301. They agreed that Study 302 was positive and met its primary endpoint Clinical Dementia Rating Sum of Boxes [CDR-SB] score at week 78 but expressed concerns about the weight of the evidence and its clinical meaningfulness. The one committee member who voted "Yes" noted that, Study 302 met its primary endpoint and showed positive trends independently. Please see the transcript for details of the Committee's discussion.*

3. **DISCUSSION:** The primary evidence of effectiveness presented in support of aducanumab for the treatment of Alzheimer's disease is provided by Study 302. Study 103 is presented as supportive evidence of aducanumab's effectiveness. Discuss the evidence of effectiveness provided by Study 103.

Committee Discussion: *Collectively, the Committee agreed that Study 103 was designed primarily as a safety and tolerability study and does not support the positive findings shown in Study 302. The Committee conveyed that the trial was too small to demonstrate efficacy, and the dose response effect did not mirror the positive results shown in Study 302 for some outcomes. In particular, a few committee members recognized the different p-values in patients treated with a high-dose regimen (10mg/kg). The Committee members noted that the high-dose regimen initially yielded a 0.04 p-value, but strikingly increased to 0.095 when patients on concomitant Alzheimer's medications were excluded; hence, Study 103 was clinically insignificant and did not provide supportive evidence of aducanumab's effectiveness. Please see the transcript for details of the Committee's discussion.*

4. **VOTE:** Does Study 103 provide supportive evidence of the effectiveness of aducanumab for the treatment of Alzheimer’s disease? YES/NO/UNCERTAIN

Vote Results: Yes: 0 No: 7 Uncertain: 4

***Committee Discussion:** A majority of the committee members voted “No”, that Study 103 did not provide supportive evidence of the effectiveness of aducanumab for the treatment of Alzheimer’s disease. These members argued that Study 103 was a prerequisite trial for other trials and should not be interpreted in the context of achieving clinical endpoints because the study itself was not powered to do so. The remaining members were uncertain as to whether Study 103 provided supportive evidence of the effectiveness of aducanumab due to the size of the trial and the purpose of the study. Like their colleagues, they too agreed that Study 103 was not designed to measure efficacy nor was it intended to capture evidence of effectiveness. Please see the transcript for details of the Committee’s discussion.*

5. **DISCUSSION:** The application presents evidence in support of effects on the pathological hallmarks of Alzheimer’s disease, including effects on amyloid beta, tau, and downstream markers of neurodegeneration, using multiple assessment modalities. Discuss the impact of these results.

***Committee Discussion:** The Committee agreed that the data shown provided clear evidence that aducanumab cleared amyloid plaques and reduced tau deposits in the brain. However, the Committee was not persuaded that the clearing of these neurodegenerative aggregated proteins correlated with cognitive improvement. The Committee recommended that there should be substantial evidence relating specific biomarkers to disease progression before there is a determination that the clearance/reduction of these biomarkers are truly related to clinical benefit (cognitive improvement). Please see the transcript for details of the Committee’s discussion.*

6. **VOTE:** Has the Applicant presented strong evidence of a pharmacodynamic effect on Alzheimer’s disease pathophysiology? YES/NO/UNCERTAIN

Vote Results: Yes: 5 No: 0 Uncertain: 6

***Committee Discussion:** A marginal majority of the committee members were uncertain as to whether the Applicant presented strong evidence of a pharmacodynamic effect on Alzheimer’s disease pathophysiology. These members indicated that the Applicant failed to show the correlation between the biomarkers and clinical effects. Although the members were convinced of aducanumab’s pharmacodynamic effects on amyloid plaques, they noted that the data associated with tau deposits were “murky”. In addition, they expressed uncertainties as to whether the biomarkers shown are true indicators for Alzheimer’s disease and urged the Applicant to study other biomarkers (proteopathies) that may have played a role in this setting. The committee members who voted “Yes” indicated that their vote coincides with the knowledge of aducanumab’s pharmacodynamic effects on the biomarkers (tau deposits and amyloid plaques) but they noted that the data failed to demonstrate that*

amyloid and tau are the sole biomarkers affected. Please see the transcript for details of the Committee's discussion.

7. **DISCUSSION:** Study 301 was a negative study. Post hoc exploratory analyses were conducted in order to achieve maximum understanding of the partially discordant results of Study 301 and Study 302, and to determine if this understanding precludes independent consideration of Study 302. Additional contribution to the understanding of aducanumab's pharmacological activity and clinical effects is provided by the results of Study 103. In light of the exploratory analyses that were conducted and the results of Study 103, discuss the impact of the results of Study 301 on the consideration of the results of Study 302.

Committee Discussion: Collectively, the Committee agreed that both studies 301 and 302 were well design phase 3 clinical trials. However, the committee members found it challenging to interpret the results of Study 302 independently without considering the negative outcome of Study 301, even with the data shown in Study 103. The members agreed that the post-hoc analysis (Study 103), which was originally designed as a safety trial, did not provide justification for overriding the data shown in Study 301 nor did it confirm the positive outcomes demonstrated in Study 302. Please see the transcript for details of the Committee's discussion.

8. **VOTE:** In light of the understanding provided by the exploratory analyses of Study 301 and Study 302, along with the results of Study 103 and evidence of a pharmacodynamic effect on Alzheimer's disease pathophysiology, is it reasonable to consider Study 302 as primary evidence of effectiveness of aducanumab for the treatment of Alzheimer's disease?
YES/NO/UNCERTAIN

Vote Results: Yes: 0 No: 10 Uncertain: 1

Committee Discussion: Almost all of the committee members voted "No", agreeing that it is not reasonable to consider Study 302 as primary evidence of effectiveness of aducanumab for the treatment of Alzheimer's disease. These members were not persuaded by the analyses provided and expressed their reluctance to suggest approval of aducanumab for the treatment of Alzheimer's disease due to the insubstantial evidence shown. In addition, these members expressed the difficulty for them to draw a conclusion on the information provided due to un-addressed criticisms provided by the statistical analysis of the studies. The one member who was uncertain on this question noted that Study 302 is positive, and Study 103 provided some additional evidence along with the evidence shown by the biomarkers. Please see the transcript for details of the Committee's discussion.

The meeting was adjourned at approximately 5:05 p.m. Eastern Time.