Food and Drug Administration
Center for Drug Evaluation and Research
Final Summary Minutes of the Peripheral and Central Nervous System Drugs Advisory Committee Meeting

Location: FDA and invited participants attended the meeting at FDA White Oak Campus, Building 31 Conference Center, the Great Room (Rm. 1503), 10903 New Hampshire Avenue, Silver Spring, Maryland. The public participated via an online teleconferencing and/or video conferencing platform, and the meeting presentations were heard, viewed, captioned, and recorded through an online video conferencing platform.

Topic: The Committee discussed biologics license application 761248, for donanemab solution for intravenous infusion, submitted by Eli Lilly and Co., for the treatment of early symptomatic Alzheimer's disease.

These summary minutes for the June 10, 2024 meeting of the Peripheral and Central Nervous System Drugs Advisory Committee of the Food and Drug Administration were approved on July 15, 2024.

I certify that I attended the June 10, 2024 meeting of the Peripheral and Central Nervous System Drugs Advisory Committee (PCNS) of the Food and Drug Administration and that these minutes accurately reflect what transpired.

/s/	**/s/**
Jessica Seo, PharmD, MPH	Thomas J. Montine, MD, PhD
Designated Federal Officer, PCNS	Chairperson, PCNS

Summary Minutes of the Peripheral and Central Nervous System Drugs Advisory Committee Meeting
June 10, 2024

The Peripheral and Central Nervous System Drugs Advisory Committee (PCNS) of the Food and Drug Administration, Center for Drug Evaluation and Research, met on June 10, 2024. FDA and invited participants attended the meeting at FDA White Oak Campus, Building 31 Conference Center, the Great Room (Rm. 1503), 10903 New Hampshire Avenue, Silver Spring, Maryland. The public participated via an online teleconferencing and/or video conferencing platform, and the meeting presentations were heard, viewed, captioned, and recorded through an online video conferencing platform. Prior to the meeting, the members and temporary voting members were provided the briefing materials from the FDA and Eli Lilly and Company. The meeting was called to order by Thomas J. Montine, MD, PhD (Chairperson). The conflict-of-interest statement was read into the record by Jessica Seo, PharmD, MPH (Designated Federal Officer). There were approximately 2872people in attendance. There was a total of 21 Open Public Hearing (OPH) speaker 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 761248, for donanemab solution for intravenous infusion, submitted by Eli Lilly and Co., for the treatment of early symptomatic Alzheimer's disease.

Attendance:

Peripheral and Central Nervous System Drugs Advisory Committee Members Present (Voting): Merit E. Cudkowicz, MD; Thomas J. Montine, MD, PhD (*Chairperson*); Tanya Simuni, MD, FAAN

Peripheral and Central Nervous System Drugs Advisory Committee Members Not Present (Voting): Robert C. Alexander, MD; Liana G. Apostolova, MD, MSc, FAAN; Richard J. Kryscio, PhD; David Weisman, MD

Peripheral and Central Nervous System Drugs Advisory Committee Member Present (Non-Voting): Paul M. Kirsch (*Industry Representative*)

Temporary Members (Voting): Cynthia Carlsson, MD, MS; Sarah Dolan (*Acting Consumer Representative*); Nilüfer Ertekin-Taner, MD, PhD; Dean Follmann, PhD; Costantino Iadecola, MD; Colette C. Johnston (*Patient Representative*); Kathleen L. Poston, MD, MS; Daniel Press, MD

FDA Participants (Non-Voting): Peter Stein, MD**;** Teresa Buracchio, MD; Paul Lee, MD; Sally Yasuda, MS, PharmD; Kevin Krudys, PhD

Designated Federal Officer (Non-Voting): Jessica Seo, PharmD, MPH

Open Public Hearing Speakers Present: Dan Clinton; Rafik and Patricia Bishara; Sue and Jim Sirois; Joanne Pike, DrPH (Alzheimer's Association); Nina Zeldes, PhD (Public Citizen's Health Research Group); John F. O'Connor; George Vradenburg (UsAgainstAlzheimer's); Judy Butler, MS and Adriane Fugh-Berman, MD (PharmedOut); Michelle Papka, PhD; Ian N. Kremer, JD (LEAD Coalition); Sandra Carlino; James Taylor (Voices of Alzheimer's); James Schmidt; Kathryn Rigby; Curtis P. Schreiber, MD (Missouri Memory Center); Marwan Sabbagh, MD, FAAN, FANA; Susan Peschin, MHS (Alliance for Aging Research); John Dwyer (Global Alzheimer's Platform Foundation); Myra Solano Garcia; Tom Phillips; Maria D. Gates

The agenda was as follows:

9:00 a.m.	Call to Order and Introduction of Committee	**Thomas Montine, MD, PhD** Chairperson, PCNS
9:10 a.m.	Conflict of Interest Statement	**Jessica Seo, PharmD, MPH** Designated Federal Officer, PCNS
9:15 a.m.	FDA Introductory Comments	**Teresa Buracchio, MD** Director Office of Neuroscience (ON) Office of New Drugs (OND), CDER, FDA
9:30 a.m.	**APPLICANT PRESENTATIONS**	**Eli Lilly and Company**
	Introduction	**David Hyman, MD** Group Vice President Chief Medical Officer Eli Lilly and Company
	Donanemab Clinical Program	**Mark Mintun, MD** Group Vice President, Neuroscience R&D Eli Lilly and Company
	Efficacy Results	**John Sims, MD** Head of Medical-Donanemab Eli Lilly and Company
	Safety Results	**Melissa Veenhuizen, DVM, MS** Vice President, Global Patient Safety Eli Lilly and Company
	Treating Early Alzheimer's Disease	**Reisa Sperling, MD** Brigham and Women's Hospital Massachusetts General Hospital Harvard Medical School

10:30 a.m.	Clarifying Questions to the Applicant	
11:00 a.m.	**BREAK**	
11:15 a.m.	**FDA PRESENTATIONS**	
	Clinical Overview of Efficacy	**Kevin Krudys, PhD** Clinical Efficacy Reviewer Associate Director ON, OND, CDER, FDA
	Clinical Overview of Safety	**Natalie Branagan, MD** Clinical Safety Reviewer Division of Neurology 1 (DN1) ON, OND, CDER, FDA
12:15 p.m.	Clarifying Questions to FDA	
12:45 p.m.	**LUNCH**	
1:30 p.m.	**OPEN PUBLIC HEARING**	
2:30 p.m.	**BREAK**	
2:45 p.m.	Questions to the Committee/Committee Discussion	
5:00 p.m.	**ADJOURNMENT**	

Questions to the Committee:

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

   Committee Discussion*: In evaluating the data presented, the Committee members were in overall agreement that the available evidence supports donanemab's effectiveness for the treatment of Alzheimer's disease in the population studied. Committee members pointed to the phase 3 trial which met its pre-specified primary and key secondary endpoints, showing significant cognitive benefits and delay in disease progression.*

   In examining the evidence for effectiveness across different tau subgroups, there was some concern by Committee members about the reduced effectiveness in patients with high tau PET levels. One member noted the data indicated less clear benefits in this group, posing challenges for clinical decision-making regarding the continuation of therapy in advanced

stages of the disease. For the no/very low tau population, although these patients were excluded from the placebo-controlled trials, some members noted indirect evidence from peripheral biomarkers suggested potential benefits of donanemab in this group as well. However, other members expressed concern around extrapolating the trial results to this population. Despite the lack of direct clinical outcomes for the no/very low tau population, the majority of Committee members were in agreement that imposing a requirement for tau PET imaging would not be necessary, noting such a requirement would raise serious practical concerns and could limit access to treatment.

Please see the transcript for details of the Committee's discussion.

2. **VOTE:** Do the available data show that donanemab is effective for the treatment of Alzheimer's disease in the population enrolled in the clinical trials with mild cognitive impairment and mild dementia?
    - In determining your vote, if you believe there is efficacy across the entire population, or efficacy only in subset of patients (e.g., those with low/med and high Tau), please indicate that with a YES vote.
    - If your assessment is that efficacy has not been established in any subset of patients, then please indicate that with a NO vote. Explain the rationale for your vote. If you voted NO, please indicate in the discussion of your vote what additional data would be needed to support the effectiveness of donanemab for the treatment of Alzheimer's disease.

Vote Result: Yes: 11 No: 0 Abstain: 0

Committee Discussion: *The Committee members were unanimously in agreement that the available data show there is evidence for donanemab's effectiveness in the treatment of Alzheimer's disease in the population studied. In support of their vote, many members cited the reasons they stated previously in addressing Question 1, summarizing the cognitive benefits and delay in disease progression demonstrated in the phase 3 trial, and also highlighting the supportive biomarker data. A few Committee members also noted a need for more data to be collected on underrepresented groups and specific populations (e.g. patients with Downs Syndrome). In addition, many panel members emphasized their concerns with imposing requirements for tau PET imaging that could pose a potential barrier to treatment access.*

Please see the transcript for details of the Committee's discussion.

3. **DISCUSSION:** Discuss the dosing regimen used in the clinical trials that completed treatment based on reduction of amyloid plaques on PET imaging, and if there are scientific and/or clinical considerations that may factor into a decision to stop or continue dosing with donanemab if approved.

Committee Discussion*: The Committee members were in agreement that the dosing regimen guided by reduction of amyloid plaques on PET imaging was an innovative component of the clinical trial design that could provide potential benefits if adapted to clinical practice. One*

member pointed to the ability to discontinue treatment potentially enhancing patient compliance and motivation. Another member noted potential benefits in reducing health care system burden and helping increase access, pointing to infusion capacity at hospitals as a rate-limiting step for being able to administer therapies such as donanemab. However, members were in agreement that more long-term data is needed to address questions on duration of amyloid clearance, how frequently patients would need to be monitored after stopping donanemab, when treatment should be re-initiated, and potential adverse effects of stopping and restarting therapy.

Please see the transcript for details of the Committee's discussion.

4. **DISCUSSION:** Discuss the overall benefit-risk assessment of donanemab for the treatment of Alzheimer's disease. If the available evidence supports a benefit, discuss if the risks appear to be acceptable given the observed treatment benefit and if there are subgroups of patients for whom the benefit-risk would be more or less favorable**.**

   Committee Discussion*: The Committee members were in general agreement that the overall benefit-risk assessment for donanemab in the treatment of Alzheimer's disease is positive, with several members highlighting the value of slowing disease progression to patients and their caregivers. Members also acknowledged risks such as amyloid related imaging abnormalities (ARIA) that need careful management. Committee members discussed the difference between ApoE4 heterozygotes and non-carriers where donanemab has demonstrated a significant clinical benefit and lower incidence of severe side effects compared to ApoE4 homozygotes who face a higher risk of ARIA but saw clinical benefits that were less clear. Members also discussed the uncertainty in the benefit-risk profile for the low/no tau subgroup where donanemab's efficacy is also less clear due to lacking data. It was also noted there was insufficient data on underrepresented groups and therefore further research was recommended for these populations. Several members emphasized the importance of individualized treatment decisions between patients and their providers based on genetic profiles, patient preferences, and specific risk factors.*

   Please see the transcript for details of the Committee's discussion.

5. **VOTE:** Do the benefits outweigh the risks of donanemab in the treatment of AD in the population enrolled in the clinical trials with mild cognitive impairment and mild dementia?
   - Explain the rationale for your vote.
   - If you voted NO, provide recommendations for additional data or analyses that may support a conclusion that the benefits outweigh the risks.

   Vote Result: Yes: 11 No: 0 Abstain: 0

   Committee Discussion: *The Committee members were unanimously in agreement that the benefits of donanemab outweigh its risks in the treatment of Alzheimer's disease for the population enrolled in the clinical trials. In support of their vote, many members cited the reasons they stated previously in addressing Question 4, noting that while donanemab presents risks, particularly with ARIA, these can be managed with appropriate safety*

measures and the potential benefit in slowing disease progression supports donanemab use in the trial population. Some members encouraged continued surveillance and additional data and analysis on underrepresented groups and special populations. Other members also emphasized appropriate education and training in healthcare systems as well as risk mitigation measures for those populations.

Please see the transcript for details of the Committee's discussion.

The meeting was adjourned at approximately 3:55pm ET.