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: Please note that due to the impact of this COVID-19 pandemic, all meeting participants joined this advisory committee meeting via an online teleconferencing platform.

Topic: The committee discussed supplemental biologics license application (sBLA) 761269/s-001, for LEQEMBI (lecanemab) solution for intravenous infusion, submitted by Eisai, Inc., for the treatment of Alzheimer's disease, initiated in patients with mild cognitive impairment or mild dementia stage of disease. This product was approved under 21 CFR 314.500 (subpart H, accelerated approval regulations) for the treatment of Alzheimer's disease. Confirmatory studies are studies to verify and describe the clinical benefit of a product after it receives accelerated approval. The committee discussed the confirmatory study, BAN2401-G000-301, conducted to fulfill post-marketing requirement 4384-1 detailed in the January 6, 2023, approval letter, available at https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2023/761269Orig1s000ltr.pdf.

These summary minutes for the June 9, 2023 meeting of the Peripheral and Central Nervous System Drugs Advisory Committee of the Food and Drug Administration were approved on June 30, 2023.

I certify that I attended the June 9, 2023 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/
Jessica Seo, PharmD, MPH
Designated Federal Officer, PCNS

/s/
Robert C. Alexander, MD
Acting Chairperson, PCNS

Final Summary Minutes of the Peripheral and Central Nervous System Drugs Advisory Committee Meeting
June 9, 2023

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 9, 2023. 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 from the FDA and Biogen, Inc. The meeting was called to order by Robert C. Alexander, MD (Acting Chairperson). The conflict-of-interest statement was read into the record by Jessica Seo, PharmD, MPH (Designated Federal Officer). There were approximately 1881 people online. 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 supplemental biologics license application (sBLA) 761269/s-001, for LEQEMBI (lecanemab) solution for intravenous infusion, submitted by Eisai, Inc., for the treatment of Alzheimer's disease, initiated in patients with mild cognitive impairment or mild dementia stage of disease. This product was approved under 21 CFR 314.500 (subpart H, accelerated approval regulations) for the treatment of Alzheimer's disease. Confirmatory studies are studies to verify and describe the clinical benefit of a product after it receives accelerated approval. The committee discussed the confirmatory study, BAN2401-G000-301, conducted to fulfill post-marketing requirement 4384-1 detailed in the January 6, 2023, approval letter, available at https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2023/761269Orig1s000ltr.pdf.

Attendance:

Peripheral and Central Nervous System Drugs Advisory Committee Members Present (Voting): Robert C. Alexander, MD (*Acting Chairperson*); Merit E. Cudkowicz, MD

Peripheral and Central Nervous System Drugs Advisory Committee Members Not Present (Voting): Liana G. Apostolova, MD, MSc, FAAN; Richard J. Kryscio, PhD; Michelle M. Mielke, PhD; Thomas J. Montine, MD, PhD

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

Temporary Members (Voting): Dean Follmann, PhD; Colette Johnston (*Patient Representative*); Klaus Romero, MD, MS, FCP; Tanya Simuni, MD, FAAN

FDA Participants (Non-Voting): Teresa Buracchio, MD; Laura Jawidzik, MD; Sally Yasuda, MS, PharmD

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

Open Public Hearing Speakers Present: Stephen Salloway, MD, MS; George Vradenburg (UsAgainstAlzheimer's); Nina Zeldes, PhD (Public Citizen); Ian Kremer (LEAD Coalition); Joanne Pike, DrPH (Alzheimer's Association); Diana Zuckerman, PhD (National Center for Health Research; Susan Peschin, MHS (Alliance for Aging Research); Karyne Jones (National Caucus and Center on Black Aging, Inc.); John Dwyer (Global Alzheimer's Platform Foundation); Joanne Bridges and Jerome Bridges; Cindy Marshall, MD, DFAAGP; Reshma Ramachandran, MD, MPP, MHS (Yale Collaboration for Regulatory Rigor, Integrity, and Transparency); Claudia Padilla, MD; Patricia Bencivenga; Dona Kim Murphey, MD, PhD (Doctors for America); Doreen Monks; Zelik Bocknek and Gail Bocknek; Patricia Luiggi; Gretchen C. Wartman (National Minority Quality Forum); Ira Leffen and Mary Duda; Myra Garcia

The agenda was as follows:

Call to Order	**Robert C. Alexander, MD** Acting Chairperson, PCNS
Introduction of Committee and Conflict of Interest Statement	**Jessica Seo, PharmD, MPH** Designated Federal Officer, PCNS
FDA Introductory Remarks	**Teresa Buracchio, MD** Director (Acting) Office of Neuroscience (ON) Office of New Drugs (OND), CDER, FDA
APPLICANT PRESENTATIONS	**Eisai, Inc.**
Introduction	**Lynn Kramer, MD, FAAN** Chief Clinical Officer, Alzheimer's Disease and Brain Health (ADBH) Eisai, Inc.
Study 301 Efficacy	**Michael Irizarry, MD, MPH** Senior Vice President, Deputy Chief Clinical Officer, ADBH Eisai, Inc.
Robustness of Efficacy Results	**Shobha Dhadda, PhD** Senior Vice President, Biostatistics and Clinical Development Operations, ADBH Eisai, Inc.
Study 301 Safety	**Michael Irizarry, MD, MPH**

Clinician's Perspective	**Sharon Cohen, MD, FRCPC** Medical Director Toronto Memory Program
Conclusion	**Lynn Kramer, MD, FAAN**

Clarifying Questions to the Applicant

LUNCH

FDA PRESENTATIONS

Clinical Overview of Efficacy	**Kevin Krudys, PhD** Clinical Efficacy Reviewer Associate Director ON, OND, CDER, FDA
Statistical Overview	**Tristan Massie, PhD** Biostatistics Reviewer Division of Biostatistics 1 (DB1) Office of Biostatistics OND, CDER, FDA
Clinical Overview of Safety	**Deniz Erten-Lyons, MD** Clinical Safety Reviewer Division of Neurology 1 (DN1) ON, OND, CDER, FDA
Concluding Remarks	**Teresa Buracchio, MD**

Clarifying Questions to FDA

BREAK

OPEN PUBLIC HEARING

BREAK

Questions to the Committee/Committee Discussion

ADJOURNMENT

Questions to the Committee:

1. **DISCUSSION:** Discuss the results from Study 301 (CLARITY AD) and whether they provide evidence of clinical benefit of lecanemab for the treatment of Alzheimer's disease (AD).

   Committee Discussion*: The Committee members agreed that Study 301 (CLARITY AD) demonstrated both statistically and clinically significant benefit of lecanemab for the treatment of Alzheimer's disease. They highlighted that the study met both its primary and secondary endpoints and expressed strong support that those benefits were clinically meaningful. Several members pointed out the study was well designed and noted the robustness of the results. Some members acknowledged the small difference observed between the treatment and placebo groups and concluded that this difference was clinically meaningful in the context of the early-stage AD population that was studied, citing presentations made by the Applicant and FDA, as well as the testimony of patients and caregivers during the Open Public Hearing. Please see the transcript for details of the Committee's discussion.*

2. **VOTE:** Do the results of Study 301 (CLARITY AD) verify the clinical benefit of lecanemab for the treatment of AD?

   Vote Result: Yes: 6 No: 0 Abstain: 0

   Committee Discussion: *The Committee members were unanimously in agreement that the results of Study 301 (CLARITY AD) verified the clinical benefit of lecanemab for the treatment of AD, citing reasons given during the previous discussion. Please see the transcript for details of the Committee's discussion.*

3. **DISCUSSION:** Discuss the overall benefit/risk assessment of lecanemab for the treatment of AD. Additionally, consider the following subgroups in your assessment:
   - Apolipoprotein E (ApoE) ε4 homozygotes
   - Patients requiring concomitant treatment with anticoagulant agents
   - Patients with cerebral amyloid angiopathy

   Committee Discussion*: The Committee agreed that the overall benefit/risk assessment of lecanemab for the treatment of AD was favorable in the population studied. The members cited the following contributing factors in their assessment: similar overall tolerability and risks for death or serious adverse events (AEs) between the treatment and placebo groups, the ability to monitor those AEs, the burden and progressive nature of the disease, as well as the unmet medical need.*

   The Committee discussed three subgroups at potentially higher risk for amyloid related imaging abnormalities (ARIA) and serious events. The majority of Committee members agreed that lecanemab demonstrated benefit across multiple endpoints in patients with AD who were ApoE ε4 homozygotes. Some members recommended that ApoE ε4 status testing be performed to inform patient-physician decision-making and benefit/risk discussions. Others highlighted the potential need for increased vigilance and monitoring in this subgroup. Regarding patients requiring concomitant treatment with anticoagulant agents, the

Committee agreed that additional data was needed and provided a wide variety of recommendations for this subgroup. One member proposed that patients on anticoagulants should not be given lecanemab due to the risk for macrohemorrhage. Another member recommended that this drug be avoided in patients on chronic anticoagulant therapy. Other members advised not excluding this patient subgroup until more data are obtained to better address the uncertainty surrounding the benefit/risk. With respect to patients with cerebral amyloid angiopathy (CAA), the Committee members were generally in support of treating this subgroup with lecanemab. Some members noted the need for a robust reporting system to gather additional real-world data on lecanemab's safety in these patients, and one member recommended excluding use in patients with the CAA-related inflammation subtype. Please see the transcript for details of the Committee's discussion.

The meeting was adjourned at approximately 4:36pm ET.