

June 7, 2024

Jessica Seo, PharmD, MPH
Designated Federal Officer (DFO), AAC & PCNS
Advisory Committee Management Branch (ACMB), DFO Team 1
Division of Advisory Committee and Consultant Management (DACCM)
Center for Drug Evaluation and Research
Office of Executive Programs
U.S. Food and Drug Administration
10903 New Hampshire Ave.
Silver Spring, MD 20993-0002

RE: FDA-2024-N-1869: Peripheral and Central Nervous System Drugs Advisory Committee; Notice of Meeting; Establishment of a Public Docket

Dear Dr. Seo and the PCNS Drugs Advisory Committee Members:

The American Geriatrics Society (AGS), an organization dedicated to improving the health and quality of life of all older adults, is writing in response to the June 10th Food and Drug Administration (FDA) advisory committee meeting to review the safety and efficacy implication of donanemab's Phase 3 trial.

The AGS is a not-for-profit organization with nearly 6,000 geriatrics health professionals who are devoted to improving the health, independence, and quality of life of all older adults. Our members include geriatricians, geriatrics nurse practitioners, social workers, family practitioners, physician assistants, pharmacists, internists, and others who are pioneers in advanced-illness care for older individuals, with a focus on championing interprofessional teams, eliciting personal care goals, and treating older people as whole persons. The AGS believes in a just society, one where we all are supported by and able to contribute to communities where ageism, ableism, classism, homophobia, racism, sexism, xenophobia, and other forms of bias and discrimination no longer impact healthcare access, quality, and outcomes for older adults and their caregivers. We provide leadership to healthcare professionals, policymakers, and the public by implementing and advocating for programs in patient care, research, professional and public education, and public policy.

We understand the heavy toll of Alzheimer's disease on patients, caregivers, and their families and are supportive of the FDA approving safe and effective new treatments. However, we believe there is still a lot we do not know about the potential benefits and harms of drugs in the anti-amyloid class. We urge the Advisory Committee to take the following into consideration as it reviews the safety and efficacy data for donanemab.

Side Effects and Safety

Primarily looking at amyloid-related imaging abnormalities (ARIA), the TRAILBLAZER ALZ-2¹ study reported that 37 percent of participants receiving donanemab developed ARIA compared to 15 percent receiving the placebo. Twenty-four percent of the participants receiving donanemab developed ARIA-E (amyloid-related imaging abnormalities - edema and/or effusion) compared to two percent from placebo group. Three participants receiving donanemab had serious ARIA and subsequently died. There were zero ARIA related deaths in the placebo group. The adverse events identified in TRAILBLAZER ALZ-2 are significant and likely to be more frequent and potentially somewhat different outside the carefully controlled environment of a clinical trial.

We believe it's critical that Eli Lilly answer the following questions, as discussed in a recent JAMA editorial by Thambisetty and Howard,² before moving forward with approval, given the incomplete reporting of clinical outcomes related to the severity of ARIA and brain atrophy caused by amyloid drugs.²

- Was symptomatic ARIA associated with accelerated worsening of memory and functional abilities at the end of the trial? Currently, there is a paucity of data to help clinicians decide whether to continue these medications with clinical or radiological resolution of ARIA, and whether this will result in worsening of cognitive or functional status with or without continued dosing.
- Is there data on the outcomes of the loss of brain volume seen with donanemab and whether they relate to worsening cognitive or functional status? We would also like to see the FDA answer this question for all amyloid drugs.
- What are the findings from individual level data on the impact of repeated ARIAs? Given the high incidence of ARIA, a potentially serious adverse event, in the Phase 3 trial, it would be critically important to inform provider decisions during ARIA monitoring.

Simply put, prescribing clinicians should not be put in the position of advising people on the safety and efficacy of a given treatment absent access to complete data from the trials of that treatment. We agree with Thambisetty and Howard² that incomplete reporting of trial data before FDA approval potentially endangers people living with a disease and undermines the public's faith in clinicians. In this instance, the Advisory Committee would be relying on incomplete data when determining whether donanemab is safe and effective as a treatment for people living with Alzheimer's Disease.

Advisory Committee Recommendations to the FDA

In its deliberations about safety and efficacy, we recommend the Advisory Committee consider these additional gaps in our knowledge about donanemab:

¹ Sims JR, Zimmer JA, Evans CD, et al. Donanemab in Early Symptomatic Alzheimer Disease: The TRAILBLAZER-ALZ 2 Randomized Clinical Trial. *JAMA*. 2023;330(6):512–527. doi:10.1001/jama.2023.13239.

² Thambisetty M, Howard R. Conveying Risks of Harm in Alzheimer Disease by Amyloid Lowering. *JAMA*. Published online May 06, 2024. doi:10.1001/jama.2024.7548

- **Diversity of Patient Population.** In the donanemab TRAILBLAZER-ALZ 2 trial,¹ people of color made up less than 10 percent of participants. Black or African Americans made up only 2.9 percent, while Hispanic/Latino made up 5.7 percent of trial participants in the U.S. There continues to be underrepresentation of affected communities.

Greater granularity in the sociodemographic factors for subpopulations, particularly in age and race/ethnicity, is crucial to assess the level of diversity, equity, and inclusion and determine whether the evidence can be generalized to minoritized, disproportionately affected, or understudied populations. Considering the racial and ethnic disparities in the prevalence of AD and other dementias among the subpopulations and increasing diversity among older people,³ it is important to determine whether age, gender, and racial and ethnic representation in trials is sufficient to support generalizability. Existing large disparities in access to AD diagnosis and care must not be exacerbated by therapeutics tested in non-representative participant populations. We urge the Advisory Committee to advise FDA to require Eli Lilly to make subgroup analyses publicly available and to also outline firm guidance for subgroups not represented in the trial regarding labeling and the need to collect post-release data in those subgroups.

- **Meaningful Outcomes.** The AGS prioritizes what matters most to patients, their families, and other care partners who want to know whether a treatment provides clear and important benefits to cognitive and functional ability and other key outcomes. The AGS believes that the health outcome goals of treatment and care for patients with AD are to achieve and maintain cognitive and functional stability to the maximum extent possible for the longest period possible. We currently do not have data on donanemab beyond 18-months and we believe this is a significant gap in our knowledge, particularly given incomplete reporting of the trial data.

Older persons with cognitive impairment—Mild Cognitive Impairment (MCI) or early-stage dementia—are most often managing several concurrent chronic medical conditions.⁴ While their cognitive impairment may be the dominant comorbidity, treatment outcomes need to consider the whole person, not isolated disease outcomes. To have meaningful improvement for patients, crucial health outcomes to consider include reduced symptom burden, effects on cognition and physical function, and sustained health-related quality of life.

Furthermore, due to heterogeneity in course of decline, a long pre-treatment measurement phase to define individual trajectories would also help to identify meaningful outcomes. There is also value in being able to evaluate long-term outcomes to determine the impact of amyloid removal on cognition in 5-10 years following completion of treatment. For donanemab and all drugs in this class, more information is needed about the longer-term cognitive and functional outcomes to inform discussion of the potential benefits and harms that prescribing clinicians will have with their patients.

³ Matthews KA, Xu W, Gaglioti AH, et al. Racial and Ethnic Estimates of Alzheimer's Disease and Related Dementias in the United States (2015-2060) in Adults Aged ≥65 Years. *Alzheimers Dement.* 2019;15(1):17-24. doi:10.1016/j.jalz.2018.06.3063.

⁴ Clague F, Mercer SW, McLean G, Reynish E, Guthrie B. Comorbidity and Polypharmacy in People with Dementia: Insights from a Large, Population-Based Cross-Sectional Analysis of Primary Care Data. *Age and Ageing.* 2016;46(1):33-39. doi:10.1093/ageing/afw176.

Potential FDA Approval

We recognize that the role of the Advisory Committee is to review the safety and efficacy data for donanemab and make a recommendation to the FDA as to whether it should be approved. In light of the gaps we have identified, we recommend that the FDA:

- Carefully describe indications as well as the monitoring and capacity of those monitoring the agent in the prescribing information.
- Consider putting donanemab under a Risk Evaluation and Mitigation (REM) strategy to ensure that there is extra focus on preventing, monitoring, and/or managing a specific serious risk.
- Ensure that the approved label and marketing materials include information about who was EXCLUDED from the donanemab clinical trial since no safety and efficacy data is available for these populations.

* * *

Thank you for the opportunity to share our concerns. We would be pleased to answer any questions you may have. Please contact Alanna Goldstein, agoldstein@americangeriatrics.org.

Sincerely,



Mark Supiano, MD
President



Nancy E. Lundebjerg, MPA
Chief Executive Officer