



Peripheral and Central Nervous System Drugs Advisory Committee
Food and Drug Administration
10903 New Hampshire Avenue
Building 31, Room 2417
Silver Spring, Maryland 20993-0002

May 23, 2024

RE: Peripheral and Central Nervous System Drugs Advisory Committee Meeting on Donanemab (FDA-2024-N-1869)

Dear Members of the Advisory Committee:

On behalf of the Alzheimer's Association, all those living with Alzheimer's disease, their caregivers, and their families, we are grateful to the Food and Drug Administration (FDA) for convening this advisory committee to discuss the approval of donanemab, an anti-amyloid treatment that reduces cognitive and functional decline in individuals with early Alzheimer's disease.

For decades, millions of Americans and their loved ones have waited for access to such a therapy while they have faced a relentless, fatal disease. There are an estimated 6.9 million Americans age 65 and older living with Alzheimer's disease. By 2050, that number is expected to rise to 12.7 million.¹

We write to make the following points regarding donanemab and the issues before FDA:

- The published Phase 3 clinical trial data regarding donanemab convincingly met the primary and all cognitive and functional secondary endpoints.²
- Donanemab's data demonstrates a meaningful clinical benefit, as well as significant benefit on a personal level for patients in need of treatments.
- Donanemab presents a similar safety profile to other mABs directed against amyloid for the treatment of Alzheimer's disease, including the already-approved Leqembi.

I. Donanemab Pivotal Trial Convincingly Achieves Primary and All Secondary Endpoints

In July 2023, researchers published the results of the Phase 3 study submitted as part of donanemab's application, TRAILBLAZER-ALZ 2, sharing the data at the 2023 Alzheimer's Association International

¹ Alzheimer's Association, Alzheimer's Disease Facts and Figures (2024), available at: <https://www.alz.org/alzheimers-dementia/facts-figures>.

² 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.

Conference (AAIC) as a featured symposium and simultaneously published in the Journal of the American Medical Association (JAMA).³

This Phase 3, double-blind, placebo-controlled study was designed to evaluate the safety and efficacy of donanemab in participants ages 60–85 years old with the presence of confirmed Alzheimer’s disease neuropathology and early symptomatic Alzheimer’s disease (either mild cognitive impairment (MCI) or mild dementia due to Alzheimer’s disease). The trial’s 1,736 participants were selected based on cognitive assessments in conjunction with amyloid plaque imaging and tau staging by positron emission tomography (PET) imaging.

The primary analysis population (n=1182) was composed of patients with an intermediate level of tau and clinical symptoms of Alzheimer’s disease, with the primary endpoint in this population showing a 35 percent slowing of decline (p<0.0001) in the integrated Alzheimer’s Disease Rating Scale (iADRS) and, in a secondary endpoint, a 36 percent slowing of decline in the Clinical Dementia Rating-Sum of Boxes, or CDR-SB) (p<0.0001).

In particular subgroups, even greater benefit was observed. For instance, in patients with MCI (as opposed to mild dementia), treatment with donanemab slowed decline, on iADRS, by 60 percent and, on CDR-SB, 46 percent. Importantly, treatment with donanemab showed cognitive and functional benefits relative to placebo regardless of baseline clinical or pathological stage of disease within the patients studied.

Overall, donanemab has demonstrated significant benefits on important cognitive and functional endpoints, easily meeting the standard for FDA’s traditional approval process.

II. Donanemab Has Demonstrated a Meaningful Benefit for Patients

A. Donanemab’s Data Demonstrates a Meaningful Clinical Benefit

It is important to emphasize that, in the context of a progressive disorder like Alzheimer’s disease, statistically significant slower progression is a meaningful clinical benefit. In working with researchers to design the Phase 3 trial for donanemab (as well as the Phase 3 trial that supported the approval of Leqembi), FDA has recognized that slowing cognitive and functional decline in a statistically significant way is an appropriate endpoint for traditional FDA approval. Further, mild cognitive impairment (MCI) and mild dementia due to Alzheimer’s disease are the phases of symptomatic illness when patients most value a delay in progression, with the delays demonstrated by donanemab for Alzheimer’s disease is equivalent to a delay in mortality for other terminal diseases.

Numerous data points demonstrate that donanemab has shown a meaningful clinic benefit for patients treated. For instance, among participants with low-medium tau, in the earlier pathological stage, 47

³ Id. See also Eli Lilly, Results from Lilly’s Landmark Phase 3 Trial of Donanemab Presented at Alzheimer’s Association Conference and Published in JAMA (July 17, 2023), available at: <https://investor.lilly.com/news-releases/news-release-details/results-lillys-landmark-phase-3-trial-donanemab-presented>.

percent of participants saw no progression at one year on the CDR-SB assessment, versus 29 percent in such patients on the placebo.⁴ Over the course of the 18-month trial, the same population of participants also saw a 39 percent lower risk of progressing to the next clinical stage of the disease. These results mean that participants treated with donanemab in this population experienced an additional 7.5 months before reaching the same level of cognitive functional decline measured by the CDR-SB when compared with patients on the placebo.

B. Personal Meaningfulness

In addition to the strong evidence showing donanemab meets the scientific standard for clinical meaningfulness, we also want to note that slowing the decline of Alzheimer's disease represents another important success: personal meaningfulness to patients, their families, and their caregivers.

While everyone experiences Alzheimer's disease differently, the trajectory of cognitive and functional decline in the disease is inevitable and the disease is fatal. For individuals living with Alzheimer's, they lose more of themselves as the disease progresses. They lose not just memories — they lose the ability to participate in the world around them. They lose their independence. All of those affected die with or from Alzheimer's disease.

For the person living with Alzheimer's disease, the diagnosis is devastating. But they are not the only ones affected. For families and friends, watching a once vibrant, curious and articulate loved one slip away can be heart-wrenching. On top of the emotional pain, these friends and loved ones become caregivers. They take on often overwhelming tasks to support the person in their daily life: bathing and dressing, feeding, keeping them safe, and making decisions for them all day, every day. Often, Alzheimer's disease caregivers do so at great expense to their own health, economic security, and emotional wellbeing.

In 2023, unpaid caregivers provided an estimated 18.4 billion hours of care valued at \$350 billion.⁵ Alzheimer's inflicts a devastating toll on caregivers. Compared with caregivers of people without dementia, twice as many caregivers of those with dementia indicate substantial emotional, financial and physical difficulties.⁶ These difficulties are not surprising. Caring for a person with Alzheimer's poses unique challenges. Individuals with Alzheimer's require increasing levels of supervision and person-centered care as the disease progresses. People in the middle to later stages of Alzheimer's experience losses in judgment, orientation, and the ability to understand and communicate effectively. The personality and behavior of a person with Alzheimer's are affected as well, and these changes are often among the most challenging for family caregivers and can often lead to placement in a long-term care community.⁷

When considering last year's FDA decision-making regarding traditional approval of Leqembi, the Alzheimer's Association sought feedback from current and former members of the Early Stage Advisory

⁴ Supra n. 2.

⁵ Supra n. 1.

⁶ Id.

⁷ Id.

Group, a group of individuals living with the disease, to gain their perspective on meaningfulness and new treatments.⁸ Overall, individuals living with Alzheimer's disease felt optimistic and enthusiastic about the development of new treatments and the idea that more treatments would be available soon. In the early stage of the disease, when skills and cognition are entirely or mostly intact, one additional day of independence and autonomy might be meaningful enough for one person, whereas others would be satisfied with a month or a year. As one person living with Alzheimer's disease expressed:

“This is a time of innovation and dedicated research that was not as prevalent in previous years. This brings TRUE HOPE for the first time in my life that maybe I can preserve my cognition and potentially have a high quality of life for a longer time. Just think about it. To be able to recognize family and friends, take care of myself, revel in the simple joys like taking a walk, hugging my grandson and watching him grow, laughing with my daughters, holding my husband's hand. All this is and so much more is truly priceless!” — Deb J., living with Alzheimer's⁹

Participants in the survey acknowledged the importance of considering safety and side effects, yet they expressed a willingness to take risks for potentially significant benefits. Notably, they emphasized the need for researchers and regulators to consider personal meaningfulness as a component of their decision making process and to provide information and access to treatments for all individuals living with Alzheimer's disease.¹⁰

III. Donanemab's Safety Profile Is In Line with other FDA-Approved Treatments and mABs Directed Against Alzheimer's Disease

The safety and well-being of people living with Alzheimer's disease is the Alzheimer's Association's highest priority. We carefully monitor the results of clinical trials and regulatory actions for new Alzheimer's treatments to ensure that our position on any individual treatment appropriately reflects both scientific and patient-centered views of the appropriate balance between risks and benefits. We understand that individuals have difficult decisions when faced with an unrelenting and fatal disease with no cure and their preferences will appropriately vary from person to person based on their unique perspectives and circumstances. Individuals should talk with their doctors to develop a treatment plan that is right for them, including weighing the benefits and risks of all approved therapies.

As with other anti-amyloid treatments in this class of drugs, and indeed all FDA-approved treatments, donanemab does have side effects. We are confident that the side effect profile for this treatment is, on the whole, manageable and less dangerous than for many other FDA-approved medications for severe and life-threatening illnesses.

⁸ Moreno, M., et. al. Personal meaningfulness of potential FDA-approved treatments: Perspectives of individuals living with Alzheimer's disease (April 14, 2023). <https://doi.org/10.1002/alz.13079>. Available at <https://alz-journals.onlinelibrary.wiley.com/doi/10.1002/alz.13079>.

⁹ Id.

¹⁰ Id.

The Alzheimer's Association was saddened to learn that three participants with serious ARIA died during the 18 month study, in addition to one death in the placebo group. Amyloid related imaging abnormalities (ARIA) is a side effect of all current anti-amyloid mAb treatments. ARIA does not usually cause symptoms but can be serious. ARIA-E is typically a temporary swelling in areas of the brain that usually resolves over time. Some people may also have small spots of bleeding in or on the surface of the brain known as ARIA-H. If symptoms of ARIA are present, they can include headache, dizziness, nausea, confusion and vision changes. Because most people who experience ARIA do not have any symptoms, this side effect can only be confirmed through imaging, making MRI monitoring an important element of treatment management.

The Alzheimer's Association has worked closely with the medical and scientific community to better understand ARIA. In March 2024, the Alzheimer's Association established a workgroup consisting of experts in the fields of basic science, neuropathology, neuroradiology and bioethics to discuss growth, as well as current gaps, in knowledge regarding amyloid-related imaging abnormalities (ARIA). While the workgroup's discussions are currently ongoing, the preliminary objective is to equip the scientific and clinical community with a comprehensive understanding of the latest knowledge on ARIA, as well as recommend directions for future research.

This workgroup builds upon the Association's prior work regarding ARIA, including convening a workgroup of leading Alzheimer's and dementia researchers that published recommendations in 2011 on the identification, management, monitoring and risk mitigation of ARIA in anti-amyloid mAb clinical trials.¹¹ These recommendations were later incorporated into FDA guidance to study sponsors to ensure the highest safety when using these treatments.

For appropriate patients under the care of clinicians providing proper care and monitoring, ARIA risk is manageable in real-world clinical settings. No barrier should stand between patients and a treatment that has a reasonable risk-benefit ratio and significantly reduces the causative pathology.

IV. Additional Considerations for Donanemab

A. Approval of Donanemab Should Not Be Delayed for Reasons Related to Duration of Treatment.

Promisingly, the Phase 3 trial demonstrated an impressive level of clearance of amyloid plaque: amyloid plaque on average was reduced by 84 percent at 18 months of treatment, compared with a 1 percent decrease in plaque for placebo participants. In the trial, patients were able to stop treatment with donanemab once they reached amyloid clearance (a predefined criteria). At 12 months, approximately half of participants had met this threshold; at 18 months, approximately 70 percent participants had reached this threshold.

¹¹ Reisa A. Sperling, et. al. Amyloid-related imaging abnormalities in amyloid-modifying therapeutic trials: Recommendations from the Alzheimer's Association Research Roundtable Workgroup (July 2011) Available at: <https://www.sciencedirect.com/science/article/pii/S1552526011025064>

Although the possibility of amyloid plaque clearance presents an important opportunity for further research to best understand the appropriate duration of treatment, it is important to emphasize that it does not affect or qualify the successful achievement of statistically significant improvements on cognitive and functional measures.

Cessation of treatment is a significant potential benefit to patients. We are confident that clinicians will be able to adequately monitor the potential reaccumulation of amyloid plaque without reliance on frequent PET scans or other impractical approaches.

B. Access to Donanemab Should Not Be Limited by Any Additional Diagnostic Requirements.

In the Phase 3 trial, the improvement observed among the subgroup of participants with low-medium levels of tau (n=1182), was greater (35 percent on iADRS and 36 percent on CDR-SB) than it was among all amyloid-positive early symptomatic Alzheimer's disease study participants (n=1736) (22 percent on iADRS and 29 percent on CDR-SB).

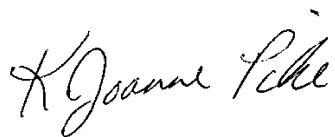
While a larger slowing of decline in the tau subgroup is a promising result that will prove opportunities for further research, it is important to recognize that access to tau imaging remains extremely limited, and therefore would certainly not be an appropriate criteria for limiting approval or coverage in any context.

Most important, in the full patient population, the declines were statistically significant and clinically meaningful. But more broadly, patients with Alzheimer's disease already struggle with access to the necessary diagnostics to confirm presence of amyloid necessary to access therapies directed at amyloid. While we are hopeful for the development of technologies to make confirming the presence of amyloid more broadly accessible, any limitations for donanemab related to tau would dramatically and inappropriately limit access without a statistically or scientifically valid justification.

Thank you for the opportunity to comment on the FDA approval of donanemab. The Alzheimer's Association would be glad to serve as a resource for the FDA as it considers donanemab, future therapies, and any other issue related to Alzheimer's disease and related dementia.

Please do not hesitate to contact Robert Egge, chief public policy officer, at regge@alz.org if we can be of additional assistance.

Sincerely,

A handwritten signature in cursive script that reads "Joanne Pike".

Joanne Pike, DrPH
President and CEO
Alzheimer's Association

Disclosures

No contribution from any organization impacts the Alzheimer's Association decision-making, nor our positions on issues related to people living with Alzheimer's, other dementia and their families. The Alzheimer's Association received 1.29% of its total 2023 contributed revenue from the biotechnology, pharmaceutical, diagnostics, and clinical research industry inclusive of 0.18% from Eli Lilly. More information is available at: [alz.org/transparency](https://www.alz.org/transparency).