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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 PCNS Drugs Advisory Committee members,

This public comment takes no formal position on the supplemental biologics license application for donanemab (BLA 761248) for the treatment of mild cognitive impairment and early dementia due to Alzheimer's disease (AD), though signatories may take a position in their separate comments. We write with a united voice to urge the Advisory Committee to consider the perspectives of people living with early AD, family and other care partners, researchers, healthcare providers, and advocates as you discuss a traditional FDA approval. We have full confidence in the FDA's impartial, rigorous, and expert review based on the merits of the Phase 3 data. FDA's world-class neuroscientists and neurologists are thoroughly equipped and unparalleled in their ability to assess the totality of evidence regarding donanemab.

The development of safe and effective therapies to prevent, delay, slow, and better manage Alzheimer's disease and related dementia (ADRD) is one of the most pressing and complex public health challenges facing our nation. One in three older adults who die have ADRD, and nearly seven million Americans have dementia due to Alzheimer's disease.¹

Donanemab does not promise to cure AD or end the scourge of dementia but, if approved by FDA, it would give clinicians and their patients a vitally important

second treatment option with substantial, clinically meaningful benefits to slow the progression of early symptomatic AD. With clear and compelling evidence, donanemab met the primary and all cognitive and functional secondary endpoints in the Phase 3 study. As borne out by the Phase 3 TRAILBLAZER-ALZ-2 (NCT04437511) trial results published in *the Journal of the American Medical Association (JAMA)* last year,ⁱⁱ donanemab substantially slowed the rate of decline on the integrated Alzheimer Disease Rating Scale (iADRS) and Clinical Dementia Rating Scale-Sum of Boxes (CDR-SB) after 18 months of treatment. Donanemab also slowed decline in instrumental activities of daily living (iADL) and multi-domain cognitive impairments of memory, orientation, judgment, and problem-solving. Both the low-medium tau and the high tau trial participants achieved these person-centered therapeutic benefits. Highlighting the urgency and utility of early detection, diagnosis, and treatment, donanemab's benefits were greatest for people in the earlier pathological stage of disease progression and the extent of benefits (compared to placebo) expanded throughout the trial's 18-month dosing period.

In short, donanemab's clinically meaningful effectsⁱⁱⁱ prolong the real time an individual enjoys their independence and quality of life – time where cognition, personality, and ability to care for oneself remain largely intact – and reduces caregiver burden. We know intuitively and through emerging robust evidence that people living with early symptomatic AD and their care partners believe these quality-of-life attributes are deeply precious and valuable.^{iv} They hold dear extended quality of life just as much as people living with other serious and life-threatening diseases such as cancer, heart failure, or HIV/AIDS. As more treatments bear positive clinical results, we are optimistic that initial successes catalyze greater advances. The community's expectations for first generation disease-modifying therapies are measured and the benefit-risk tolerance is reasonable in conjunction with recommended monitoring and management of potential side effects. While additional post-market research on subpopulations that may be especially vulnerable to ARIA is warranted, for the majority of individuals symptomatic ARIA risk is low, and decisions on the appropriateness of treatment with donanemab should be made by individuals in consultation with their physicians. We believe that a just and rational definition of clinical meaningfulness would embrace donanemab's overall 37% lower risk of progressing to the next clinical stage and (on average) nearly five and half month advantage over placebo in cognitive and functional decline for people living with early symptomatic AD.

Thank you for your consideration of these comments and for FDA's consistent commitment to illuminating the regulatory pathway for safe and effective products. For any questions or additional information, please contact Ian Kremer, Executive Director of Leaders Engaged on Alzheimer's Disease (the LEAD Coalition), at ikremer@leadcoalition.org.

Sincerely,

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CaringKind, The Heart of Alzheimer's Caregiving

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National Certification Council for Activity Professionals

National Consumers League

National Consumer Voice for Quality Long-Term Care

National Council for Behavioral Health

National Hartford Center of Gerontological Nursing Excellence

National Hispanic Council On Aging (NHCOA)

National Kidney Foundation of Wisconsin

National Minority Quality Forum

National Task Group on Intellectual Disabilities and Dementia Practices

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** Affiliations of individual researchers are for identification purposes only and do not necessarily represent the endorsement of affiliated institutions.*

ⁱ Alzheimer's Association. 2024 Alzheimer's Disease Facts and Figures
<https://www.alz.org/media/Documents/alzheimers-facts-and-figures.pdf>

ⁱⁱ 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.
<https://jamanetwork.com/journals/jama/fullarticle/2807533>

ⁱⁱⁱ Klein EG, Schroeder K, Wessels AM, et al. How donanemab data address the coverage with evidence development questions. *Alzheimer's Dement*. 2024; 20: 3127–3140. <https://doi.org/10.1002/alz.13700> <https://alz-journals.onlinelibrary.wiley.com/doi/10.1002/alz.13700>

^{iv} DiBenedetti DB, Slota C, Wronski SL, Vradenburg G, Comer M, Callahan LF, Winfield J, Rubino I, Krasa HB, Hartry A, Wieberg D, Kremer IN, Lappin D, Martin AD, Frangiosa T, Biggar V, Hauber B. Assessing what matters most to patients with or at risk for Alzheimer's and care partners: a qualitative study evaluating symptoms, impacts, and outcomes. *Alzheimers Res Ther*. 2020 Jul 30;12(1):90. doi: 10.1186/s13195-020-00659-6. PMID: 32731886; PMCID: PMC7393916.
<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7393916/>