

December 22, 2022

Janet Woodcock, M.D.
Acting Commissioner of Food and Drugs
Food and Drug Administration
10903 New Hampshire Ave
Silver Spring, MD 20993-0002

RE: Food and Drug Administration's Review of Eisai's Drug Lecanemab for Alzheimer's Disease

Dear Acting Commissioner Woodcock:

The American Geriatrics Society (AGS), an organization dedicated to improving the health and quality of life of all older adults, is writing to express our concern around the Food and Drug Administration's (FDA) upcoming review and potential approval of lecanemab for use in treating patients with mild cognitive impairment (MCI) and mild dementia due to Alzheimer's disease (AD). At this time, we do not believe there is sufficient evidence to support the accelerated approval of lecanemab. We believe it is unclear whether lecanemab meaningfully reduces progression of AD and if the potential benefits as a treatment for patients with MCI and AD outweigh the potential harms.

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 fully supportive of the FDA approving safe and effective new treatments. However, based on the available evidence, we do not support the approval of lecanemab at this time. We believe that longer trials are warranted to determine the efficacy and safety of lecanemab in MCI or mild dementia due to AD as further outlined below. We believe that if the FDA grants accelerated approval of this agent, the indications as well as the monitoring and capacity of those monitoring the agent should be carefully described in the prescribing information. The FDA could also consider putting lecanemab 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.

- **Whether treatment with lecanemab results in clinically meaningful benefit is uncertain.** While the phase 3 clinical trial Clarity AD met the primary clinical endpoint, the adjusted mean

difference of 0.45 on the Clinical Dementia Rating (CDR)–Sum of Boxes (CDR-SB) in the lecanemab group and placebo group is less than one increment of change on the scale of 0 to 18. The primary and secondary endpoint measures, along with baseline measures, suggest that the adjusted mean change in the CDR-SB score at 18 months was 1.21 and 1.66 for lecanemab and placebo, respectively. The Alzheimer’s Disease Assessment Scale (ADAS-cog14) and Alzheimer’s Disease Cooperative Study–Activities of Daily Living Scale for Mild Cognitive Impairment (ADCS-MCI-ADL) scores did not show differences that are likely to be clinically meaningful (4.14 v. 5.58, and -3.5 v. -5.53, respectively).¹ We believe that additional studies with longer treatment and follow-up may determine whether these measures will continue to separate by the treatment group. Moreover, there is evidence of response heterogeneity with certain subgroups (e.g., young-onset AD) showing no statistically significant effect. Additional studies may also clarify the impact of apolipoprotein E (ApoE) carrier status on treatment response.

From the geriatrics’ perspective of person-centered care, demonstrating improvements in what matters most to people living with AD and their family care partners—including clear benefits in functional performance and other key outcomes that are recognized by patients and care partners—would be necessary to establish true clinical relevance.

- **Side effects and safety.** Primarily looking at amyloid-related imaging abnormalities (ARIA), the studies suggest over 26 percent of participants in the lecanemab group developed ARIA. The adverse events identified in Clarity AD are meaningful and likely to be more frequent and potentially somewhat different outside the carefully controlled environment of a clinical trial. Additional studies will help to better understand the risks for adverse events associated with lecanemab use. The FDA has an important role to play in defining proper monitoring.
- **Lack of diversity in participants.** Clarity AD improved on some prior clinical trials in AD by including a larger proportion of Latinx participants, but greatly underrepresented Black persons who are disproportionately affected by AD or other dementias. However, the proportion of Black participants enrolled in Clarity AD overall was small (4.5 percent from the US).¹ In addition, while 33 percent of individuals who are 85 years of age or older have Alzheimer’s dementia,² Clarity AD has not presented disaggregated data for older age groups, including 75-85 and ≥ 85 years. 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 underrepresented, 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

¹ van Dyck CH, Swanson CJ, Aisen P, et al. Lecanemab in Early Alzheimer’s Disease. *N Engl J Med*. 2022. doi:10.1056/NEJMoa2212948 (Subgroup Analysis – Clarity AD Manuscript Supplement. Table S1 Representativeness of Study Participants)

² Alzheimer’s Association. 2022 Alzheimer’s Disease Facts and Figures. *Alzheimers Dement*. 2022;18(4):1-122. <https://www.alz.org/media/documents/alzheimers-facts-and-figures.pdf>.

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

representation in trials is sufficient to support generalizability. Existing large disparities in access to AD diagnosis and care must not be exacerbated by approval based on non-representative participant populations.

Finally, economic effects will impact the availability of resources to care for persons with dementia. While such considerations may be outside the purview of the FDA, they are particularly relevant in an accelerated approval process wherein, despite limited scientific evidence, approval is granted due to the potential for benefit. The net effect will include the unintended consequences of overstressing Medicare's limited financial reserves, and challenging health care systems—many of which are already struggling to become broadly age-friendly and dementia-capable—to divert resources to a potentially expensive treatment of uncertain value as well as added costs related to testing to establish amyloid positivity and brain MRI scans to monitor for ARIA.

Should the FDA review panel recommend accelerated approval despite these concerns, we strongly believe that lecanemab should fall under the current Centers for Medicare & Medicaid Services (CMS) coverage policy for Monoclonal Antibodies Directed Against Amyloid for the Treatment of Alzheimer's Disease that receive accelerated approval whereby Medicare will provide coverage under evidence development in the case of FDA or National Institutes of Health (NIH) approved trials and will so comment to CMS.

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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,



Michael Harper, MD
President



Nancy E. Lundebjerg, MPA
Chief Executive Officer