

June 2, 2021

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 Biogen's drug Aducanumab 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 that the Food and Drug Administration's (FDA) upcoming review and potential approval of Aducanumab for use in treating patients with mild cognitive impairment (MCI) and Alzheimer's disease (AD) is premature given the lack of sufficient evidence to support that Aducanumab reduces progression of Alzheimer's disease and that the potential benefits as a treatment for patients with MCI and AD could outweigh the potential harms.

The AGS is a not-for-profit organization comprised of 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, and internists 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. 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 are familiar with the information that has been released to date. Aducanumab, a human monoclonal antibody developed by Biogen, was assessed in two identical phase III randomized controlled trials, ENGAGE and EMERGE, planned to provide 18-month outcome data in patients with MCI and AD, all with positive amyloid PET scans. During the study, participants were given either a low or high dose of the drug. Half-way through the trials in March 2019, both ENGAGE and EMERGE were terminated after a planned interim analysis met criteria for futility. The analysis found no benefit versus the placebo at either the low or high doses. Further analysis of additional data, however, found conflicting data regarding efficacy between the two trials, with only one, EMERGE, showing a benefit in a sub-analysis of data limited to the higher dose.

We understand the heavy toll of Alzheimer's disease on patients, caregivers, and their families and are fully supportive of FDA approving safe and effective new treatments. However, based on the available evidence, we believe that approval of Aducanumab at this time is premature. We have outlined our concerns below:

- **The clinical trials of Aducanumab were incomplete.** As noted above, the two Phase III trials were halted at 50 percent completion. The independent data monitoring committee had conducted a futility analysis and found it unlikely to meet the trials' primary endpoints.
- **The clinical relevance of the positive Aducanumab findings is ambiguous.** Though the trials demonstrated a significant reduction in amyloid PET scan plaque density at one-year, clinical benefit was less certain. The increase in Clinical Dementia Rating–Sum of Boxes [CDR–SB] score, a measure of AD progression, was smaller in the 10 mg/kg subgroup ($p=0.05$) than in the placebo treated group. Although there were small changes in some other indicators, the clinical importance of these small changes is likely minimal. From the geriatrics perspective of person-centered care, demonstrating improvements in what matters most to the AD patient and their family care partners - including clear benefits in functional performance and other key outcomes - would be necessary to establish true clinical relevance. Since the measures used in the trials cannot address this key question, we consider the evidence inconclusive. Moreover, the trial duration reflects a fraction of the actual duration of the disease, and participant selection was limited to a period in disease evolution at which individual rates of progression are highly variable.
- **Reliance on a single, incomplete trial as the basis for approval.** While we understand that the FDA can approve a new drug based on evidence from a single study, regulatory guidance notes the importance of characteristics that “support the persuasiveness of a single trial in supporting the conclusion that there is substantial evidence of effectiveness.” A negative outcome in one study is as likely the true result as a positive outcome in a similar study. Further, given that the trial was halted mid-way by the data monitoring committee, moving forward with approval runs against regulatory guidance.
- **Post hoc analysis should be hypothesis generating and not used for FDA approval.** A statistical reviewer at the FDA noted that analyses based on a post hoc selection of the better of two randomized clinical trials—the one reaching statistical significance— without methods that acknowledge this purposeful choice increase the risks of inadvertently selecting data precisely because those data were consistent with the outcomes that were hoped for. For example, could the effect seen in EMERGE be ascribed to a larger decline in cognition in the placebo group?
- **This is not a side effect free drug.** There was a substantial incidence of adverse events that led to the discontinuation of the drug in the EMERGE study. In particular, 30-40 percent of individuals developed amyloid-related imaging abnormalities (ARIA), including edema and microhemorrhages. While these can be asymptomatic, they can be severe in some cases.
- **There has been no peer-reviewed publication on this drug to date.** Peer review is important to ensuring that research is trustworthy, the methodology is sound, and that medical treatments are safe and effective.
- **A related open question** is about trial participants' demographic characteristics. It is important to determine whether age, gender and racial and ethnic representation is sufficient to support generalizability to all older adults with AD. Existing large disparities in access to AD diagnosis and care must not be exacerbated by approval based on non-representative participant populations;

a recent Phase II trial publication of a related anti-amyloid immunotherapy reported that only 3% of trial participants were Black and 1% were Asian.¹

Finally, if despite these concerns the FDA review panel recommends its approval, we strongly encourage that the eligibility criteria appropriately address these concerns. Additional considerations are the unintended consequences of over stressing Medicare's limited financial reserves, and of challenging health care systems, many of which are already struggling to become broadly age-friendly and dementia-capable, to divert precious resources to an expensive treatment of uncertain value.² Questions have already been raised by thoughtful analysts about the cost-effectiveness of aducanumab as a therapeutic agent; administering the treatment as a whole will carry substantial added costs, such as testing to establish amyloid-positivity (amyloid PET scans, CSF biomarkers, or other proprietary tests), and repeated brain MRI scans to monitor for the common ARIA adverse effects. Carefully delineating the criteria for standardizing treatment will be extremely important, while at the same time ensuring access to all older AD patients who meet the stringent eligibility criteria.

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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,



Peter Hollmann, MD
President



Nancy E. Lundebjerg, MPA
Chief Executive Officer

¹ Mintun MA, Lo AC, Duggan Evans C, et al. Donanemab in Early Alzheimer's Disease. *New England Journal of Medicine* 2021;384:1691-704.

² Aducanumab for Alzheimer's Disease: Effectiveness and value. Draft evidence report, May 5, 2021. https://icer.org/wp-content/uploads/2020/10/ICER_ALZ_Draft_Evidence_Report_050521.pdf