Testimony Before the FDA's Peripheral and Central Nervous System Drugs Advisory Committee Regarding Donanemab

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Public Citizen opposes approval of the biologics license application of donanemab for the treatment of Alzheimer's disease because the evidence for the drug's benefits does not outweigh its substantial risks. The essential issue is not the specifics of the prescribing information, but whether the drug should be approved to begin with.

In the pivotal clinical trial, there was a statistically significant difference between the donanemab and placebo groups for the primary endpoint (the change from baseline in the integrated Alzheimer's Disease Rating Scale at 76 weeks). However, the difference in both of the primary endpoint populations was only about three points on a scale that ranges from 0 to 144.[1] We view this 2% difference between groups as unlikely to be clinically meaningful. The statistically significant differences between the groups in secondary endpoints were also small and of uncertain clinical significance.

In contrast to the weak evidence for clinical benefit, the safety data for donanemab are very concerning. For instance, 36% of subjects treated with donanemab developed amyloid-related imaging abnormalities (ARIA), compared with 14% of subjects in the placebo group.[2] About 24% of donanemab-treated subjects experienced more than one treatment-emergent event of ARIA-E, and for approximately 15% of subjects, clinical symptoms of ARIA-E did not resolve. At least three of the 19 deaths in the treatment group were associated with ARIA, as compared with 0 of 16 deaths in the placebo group.[3]

[1] Food and Drug Administration. FDA briefing document, BLA# 761248, Drug name: donanemab-azbt, Peripheral and Central Nervous System (PCNS) Advisory Committee Meeting. June 10, 2024. https://www.fda.gov/media/179166/download. Accessed June 10, 2024.
[2] *Id.* PDF p. 36, p. 38.
[3] *Id.* PDF p. 32.

Importantly, the percentage of subjects in the donanemab trial who developed ARIA was higher than in the pivotal trial for lecanemab.[4] It is very concerning when 21% of subjects receiving drug treatment for Alzheimer's disease develop ARIA, as was the case in the lecanemab trial, and even more concerning when 36% of subjects develop ARIA, as was the case in the donanemab trial.

Other disturbing treatment effects of donanemab are the increase in ventricular volume and the decrease in whole brain volume.[5] Both of these changes can be associated with Alzheimer's disease progression.[6]

Additionally, although the prevalence of Alzheimer's disease is higher in Black than White individuals, 92% of the subjects in the pivotal clinical trial were White.[7,8]

Public Citizen's Health Research Group opposed the approval of aducanumab, we opposed the approval of lecanemab, and now we oppose the approval of donanemab. We urge the advisory committee to vote "No" on both voting questions and recommend to the FDA that the biologics license application for donanemab not be approved.

[4] Food and Drug Administration. FDA Briefing document, sBLA# 761269/s-001, drug name: lecanemab-irmb; Peripheral and Central Nervous System (PCNS) Drugs Advisory Committee Meeting. June 9, 2023. https://www.fda.gov/media/169263/download. Accessed June 10, 2024.
[5] Food and Drug Administration. FDA briefing document, BLA# 761248, Drug name: donanemab-azbt, Peripheral and Central Nervous System (PCNS) Advisory Committee Meeting. June 10, 2024. https://www.fda.gov/media/179166/download. Accessed June 10, 2024.
[6] STAT News. Anti-amyloid drugs and the mystery of treatment-associated brain shrinkage. November 29, 2022. https://www.statnews.com/2022/11/28/anti-amyloid-drugs-treatment-associated-brain-shrinkage/. Accessed June 10, 2024.
[7] Food and Drug Administration. FDA briefing document, BLA# 761248, Drug name: donanemab-azbt, Peripheral and Central Nervous System (PCNS) Advisory Committee Meeting. June 10, 2024. https://www.fda.gov/media/179166/download. Accessed June 10, 2024.
[8] 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.