



June 8, 2023

Food and Drug Administration,
10903 New Hampshire Avenue
Silver Spring, MD 20993

Docket No. FDA-2023-N-1114

PharmedOut, an evidence-based prescribing project at Georgetown University Medical Center, urges the FDA to reject Leqembi (lecanemab) for full approval. The sponsors — and the patient advocacy groups funded by those sponsors — persist in passionately defending a fantasy: that Leqembi can prevent a patient from slipping into the most difficult stages of the disease. That assertion is based on unsubstantiated hope. It is far more likely that Leqembi will harm rather than help Alzheimer's patients.

The results of the [CLARITY AD](#) trial do not support clinical benefit of Leqembi. Not a single patient in this trial got better.¹ Patients in both the treatment and placebo groups continued to decline, and any difference between them was not clinically meaningful. Specifically, participants had an average baseline cognitive score of 3.2 on a scale of 0 to 18 (higher scores indicate greater impairment). At the end of the trial, the average treatment score for treated patients was 4.41 compared to 4.86 for the placebo group. Although statistically significant, the difference in scores was clinically insignificant: a minimal clinically meaningful difference is considered to be between 1.0 and 2.5 points, and the difference in this trial was 0.45. Moreover, there was not actual improvement but only a slight difference in the extent of worsening, one that neither patients nor family would notice.

Leqembi reduces amyloid in the brain, but the relationship between amyloid and Alzheimer's is complicated, and reducing amyloid has never improved any dementia symptoms. The lack of any actual clinical improvement may explain why the sponsors attempt to spin the amyloid-busting effects as a "disease-modifying" effect. This is a red herring.

The difference in outcomes between treatment and placebo groups is very small, just 2.5% on the 18-point cognitive scale. The better-sounding "27% slowing of decline" touted by the sponsors and their paid consultants comes from calculating the [relative difference](#) between the two groups.² Based on a slope analysis of the relative difference, the sponsors assert that the difference between placebo and treatment groups can be interpreted as a [5.3 month delay](#) in clinical deterioration after 18 months.³ By extrapolating, they projected that this difference will increase to 7.5 months after 25 months of treatment.

There are several problems with this interpretation. First, there is no evidence that any treatment effect will progress linearly in a positive direction; the effect could slow, stop, or reverse. Second, if there is no clinically meaningful difference, a statistical difference means nothing. But that doesn't stop conflicted patient advocacy groups, including the



[Alzheimer's Association](#)⁴ and the [Alliance for Aging Research](#),⁵ from using the 5 month delay as a talking point for mobilizing support for Leqembi.

Tellingly, the serious harms associated with Leqembi are often omitted from these advocacy groups' comments. Lecanemab causes brain bleeding and swelling which is called ARIA (amyloid-related imaging abnormalities). Hemorrhages occurred in 17.3% of patients treated with Leqembi. Brain swelling, edema, occurred in 12.6%. Patient advocacy groups and consultants minimize these toxicities by suggesting that Leqembi removes the amyloid surrounding brain blood vessels in a way similar to 'scraping paint off of a wall'. However, it actually acts more like a sledgehammer — taking down the wall as well as the paint. Monoclonal antibodies destroy amyloid and weaken the integrity of blood vessels in the brain.

[Three patients taking Leqembi in clinical trials](#) from brain bleeds.⁶ This suggests a rate of [1 to 2 deaths per 1,000 patients](#) — and that's in the healthier-than-normal clinical trial population.⁷ The death rate is likely to be far higher in a general population.

For a treatment that is touted as disease-modifying it is highly concerning that Leqembi is associated with [brain atrophy](#), shrinkage in brain volumes, and increases in the fluid-containing ventricles.⁸ Detailed data has been closely held by Eisai and not shared with researchers, even when [requested](#).⁹

A systematic review and meta-analysis of [accelerated brain volume loss](#) caused by anti- β -amyloid drugs included that 18 months on the highest trial dose of Leqembi accelerated whole brain atrophy by 28% and enlarged ventricles by 36% compared to placebo.¹⁰ The whole brain volume loss was 5.2 mL — more than a teaspoon of brain matter. Patients who develop ARIA early in treatment may go on to develop brain volume loss and ventricles that take on more fluid.

Shrinking the brain will hurt, not help dementia patients. This inconvenient fact may explain the sponsors' and advocates' utter silence on the issue. When cornered, researchers may say that the brain shrinkage is related to loss of amyloid, but that's not true. The amount of brain volume lost is [more than 1000 times](#) the total amount of amyloid in the brain of an Alzheimer's patient.¹¹

The [long-term consequence](#) of drug-induced volume loss to brain health has not been investigated, but it is reasonable to expect that drug-induced brain shrinkage is associated with poorer outcomes.¹²

Please don't use a standard of hope to recommend full FDA approval for any drug. The confirmatory trial does not support clinical benefit of Leqembi, and the harms certainly outweigh the alleged minimal slowing of decline for patients. Patients and their families deserve better than the false hope offered by Leqembi. This committee should not accept the data presented as sufficient for proving clinical benefit. Doing so would create an abysmal standard for future Alzheimer's drugs applying for approval.



Please vote to reject this application for full approval of Leqembi.

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- ¹ Van Dyck, C, et al. Lecanemab in Early Alzheimer's Disease. New England Journal of Medicine. 2023;388(9). doi:10.1056/NEJMoa2212948
 - ² Schrag, Matthew. "The much trumpeted "27% slowing" is a relative value - the absolute difference on this test was 2.5%. In this image, I have re-scaled the result from the NEJM paper to include the absolute difference. [Values approximated using a graph extractor]." November 3, 2022, 2:48am. Tweet
 - ³ BIOARTIC. Clarity AD: A Phase 3 Placebo-Controlled, Double-Blind, Parallel-Group, 18-Month Study Evaluating Lecanemab in Early Alzheimer's Disease [Internet]. 2022 [cited 2023 May 31]. Available from: <https://bioarctic.se/en/wp-content/uploads/sites/2/2021/03/bioarctic-annual-report-2020.pdf>
 - ⁴ Alzheimer's Association, Individuals Living with Alzheimer's urge FDA to grant traditional approval for Lecanemab [Internet]. 2023 [cited 2023 May 31]. Available from: <https://www.alz.org/news/2023/urge-fda-traditional-approval-lecanemab-leqembi>
 - ⁵ Alliance advocates for Equitable Access for Alzheimer's patients seeking new treatment [Internet]. 2023 [cited 2023 May 31]. Available from: <https://www.agingresearch.org/news/alliance-advocates-for-equitable-access-for-alzheimers-patients-seeking-new-treatment/>
 - ⁶ Should people on blood thinners forego Leqembi? [Internet]. 2023 [cited 2023 Jun 7]. Available from: <https://www.alzforum.org/news/research-news/should-people-blood-thinners-forego-leqembi>
 - ⁷ Rodriguez T. Forecasting real-world usage of Lecanemab for AD treatment: An expert roundtable [Internet]. 2023 [cited 2023 May 31]. Available from: <https://www.neurologyadvisor.com/topics/alzheimers-disease-and-dementia/forecasting-real-world-usage-lecanemab-ad-treatment-expert-roundtable/>
 - ⁸ Alves F, Kalinowski P, Ayton S. Accelerated Brain volume loss caused by anti- β -amyloid drugs. Neurology. 2023;100(20). doi:10.1212/wnl.0000000000207156

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- ⁹ Alves F, Kalinowski P, Ayton S. Accelerated Brain volume loss caused by anti- β -amyloid drugs. *Neurology*. 2023;100(20). doi:10.1212/wnl.0000000000207156
- ¹⁰ Alves F, Kalinowski P, Ayton S. Accelerated Brain volume loss caused by anti- β -amyloid drugs. *Neurology*. 2023;100(20). doi:10.1212/wnl.0000000000207156
- ¹¹ Ayton S. Brain volume loss due to Donanemab. *European Journal of Neurology*. 2021;28(9). doi:10.1111/ene.15007
- ¹² Alves F, Kalinowski P, Ayton S. Accelerated Brain volume loss caused by anti- β -amyloid drugs. *Neurology*. 2023;100(20). doi:10.1212/wnl.0000000000207156