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More Alzheimer's drugs head for FDA review: what scientists are watching

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Eli Lilly and other pharma firms have begun submitting their anti-amyloid drug hopefuls for approval. But questions linger over the controversial precedent set by Biogen's aducanumab.

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When the US Food and Drug Administration (FDA) approved biotechnology firm Biogen's drug for Alzheimer's disease in June, regulators hoped to usher in a new era of treatment for the neurodegenerative condition. But the decision followed an independent advisory committee's near-unanimous vote to reject the drug, called aducanumab — and [instead divided the community](#). Some researchers think that the approval will bolster the development of drugs for treating brain disease, but others see it as a blemish on the FDA's integrity and an obstacle to progress.

Pharmaceutical company Eli Lilly in Indianapolis hopes that its antibody donanemab, which works in a similar way to aducanumab, will have a better reception. The firm plans to finish submitting its drug candidate for FDA approval in the next few months, paving the way for a decision in the second half of 2022. Meanwhile, Biogen, based in Cambridge, Massachusetts, and its partner Eisai, based in Tokyo, are racing to complete the submission of data for another competitor, lecanemab. The regulatory fate of these therapeutic hopefuls could foretell the future of Alzheimer's and [shape neurodegenerative drug development programmes](#) for years.

Following the Clinical Trials on Alzheimer's Disease (CTAD) conference last week in Boston, where researchers discussed the drug candidates, *Nature* reviews the questions everyone is asking.

Do amyloid-lowering drugs help patients?

According to the 'amyloid hypothesis' of Alzheimer's disease, the build-up of a protein called amyloid-β in the brain causes neurodegeneration. Aducanumab and its would-be competitors clear clumps of amyloid-β from the brain. But clinical trials have not meaningfully demonstrated that these therapeutics slow memory loss or cognitive decline. This is a particular point of contention for aducanumab, an antibody drug that is now on the

market for around US$56,000 per year, despite prematurely halted phase III trials and the messy data set that was submitted for approval.

Landmark

Some hope that Lilly's donanemab trials will eventually provide proof of benefit. The first of these is an 18-month phase II trial called Trailblazer-Alz that enrolled 257 people. It showed[1] that the cognitive capabilities of people who received the antibody declined more slowly than those of placebo recipients. The average difference was 3.20 points on a 144-point scale.

For Mark Mintun, senior vice-president of neuroscience research and development at Lilly, this signal is promising. Treated patients avoided around six months of cognitive decline over the course of the study, he says. With longer use of donanemab, participants might benefit even more, he speculates.

Rob Howard, a psychiatrist at University College London, is unconvinced, however. The observed 3.20-point difference is "trivial", he says. Best-case interpretations of aducanumab and lecanemab data point to similarly marginal effects. Generic donepezil — a 25-year-old Alzheimer's drug that treats the symptoms rather than the root cause of the disease — outperforms the antibodies, he adds.

Sharon Sha, a neurologist who oversees neuroscience clinical trials at Stanford University in California, says more data are needed to assess the clinical utility of these drugs. "We really need to make sure that [these antibodies] are changing the daily lives of patients or keeping them stable," says Sha, an investigator in trials of all three therapies.

One of the conditions that came with the FDA's approval of aducanumab was that Biogen run a 'confirmatory trial' ensuring that the antibody actually helps people. The biotech firm has yet to launch that trial, and the FDA gave it nine years to collect the results — a long timeline that has contributed to the uproar over the drug's approval.

For Ezekiel Emanuel, a bioethicist at the University of Pennsylvania in Philadelphia, the data need to come sooner. The accelerated approval pathway should be updated to mandate faster collection of high-quality confirmatory data, he wrote in *the Journal of the American Medical Association*[2].

Assuming that the FDA approves donanemab using the same accelerated approval pathway, Lilly, too, will have to confirm the benefit of its antibody. The pharma firm is running a 1,500-patient phase III trial called Trailblazer-Alz2 of donanemab for people in early stages of Alzheimer's. Results are due in the first half of 2023 — after the antibody's potential approval — and might provide the data needed. Another phase III trial is recruiting 3,300

patients at risk of Alzheimer's, to test whether earlier use of the antibody delays the onset of dementia. This trial will run until 2027.

The results of these studies might help to heal a divided field. "Could [the approval of aducanumab] have been done better? I think everyone agrees that this could have unfolded more effectively," Mintun says. "But as the data accumulate, people will get more and more convinced, and the divisions, I think, will disappear."

The accelerated approval of aducanumab established a precedent for others to follow. The FDA can approve Alzheimer's drugs on the basis of their ability to remove amyloid-β from the brain — without clear evidence of cognitive benefit. Pharma watchers therefore think that an accelerated approval for donanemab is likely, barring undisclosed issues regarding efficacy, safety or manufacturing.

"Of course they'll approve it," Howard says. "It's difficult to see how they can have approved aducanumab and not approve donanemab."

Donanemab's amyloid-lowering ability is not in dispute. In Trailblazer-Alz, it lowered amyloid-β levels on average by almost 80%. These data suggest that it outperforms aducanumab on amyloid clearance. Lilly has setup a head-to-head trial of donanemab and aducanumab to directly compare their amyloid-lowering capabilities.

A flashpoint in the approval of aducanumab was the FDA's decision to disregard its advisory committee's concerns about the antibody.

The agency convened this panel of experts one year ago to discuss Biogen's complicated data set. In 2019, the company halted development of aducanumab after interim analyses of two phase III trials showed that the antibody was not helping people. Months later, it reversed course and said it would seek approval on the basis of a fresh analysis of the data that hinted at cognitive benefit.

One panellist said that Biogen's statistical interpretation of its data was akin to "firing a shotgun at a barn and then painting a target around the bullet holes". Ten panellists voted against approval, and one abstained.

After the FDA approved aducanumab, three members of this committee quit in protest.

High-ranking FDA officials defended their position in prominent journals3,4 and newspapers, but the fallout has continued. Off-the-books meetings between the FDA and Biogen might have enabled the approval, *STAT News* reported in June. The federal watchdog at the Department of Health and Human Services is now reviewing the

steps that led up to the approval, and is due to release a report in 2023. Two congressional committees in the US House of Representatives are also investigating the decision.

If confirmed by the US Senate, Robert Califf, US President Joe Biden's [recent pick to head up the FDA](), will have to handle any repercussions of this decision — and decide how to move forward with accelerated approvals. But with the regulatory precedent established, there is no clear requirement for an independent advisory committee to review donanemab.

For Caleb Alexander, an internist and epidemiologist at the Johns Hopkins Bloomberg School of Public Health in Baltimore, Maryland, the need is instead reputational. "The FDA's credibility has unfortunately taken a significant hit with the management of aducanumab," says Alexander, a member of the committee that advised the FDA not to approve the drug. "If they want to salvage their credibility, they need to be sure that this new product is reviewed by an advisory committee."

The FDA initially approved aducanumab for anyone with Alzheimer's — a disease that affects more than six million people in the United States. But Biogen tested the antibody only in a subset of these patients.

After the backlash, the agency narrowed the specification to people with "mild cognitive impairment or mild dementia stage", to better match the group tested in Biogen's trials. But the drug's label, which specifies who should use it, does not stipulate that people must have evidence of amyloid build-up in their brain — a key requirement for inclusion in Alzheimer's trials.

One concern is that the FDA's guidelines put people at risk of potentially fatal side effects, for little or no chance of benefit. Aducanumab can cause brain swelling. Most patients don't experience any symptoms from this swelling, but they need regular brain scans — which are onerous and expensive — to avoid possible complications.

Lilly tested donanemab, which also causes brain swelling, in people at early stages of the disease. It measured amyloid-β, as well as levels of another protein marker of disease, called tau, to limit trial enrolment to the patients who are most likely to benefit. Mintun declined to comment on Lilly's vision for treatment eligibility. "This is a conversation I would love to have with the FDA," he says.

Howard expects another broad approval from the FDA. "It doesn't make any sense to punish Lilly and treat them differently from Biogen," he says. The onus then falls on doctors to work out how and when to use the antibody safely.

But Emanuel argues that the FDA should narrow eligibility for all anti-amyloid therapies — and ensure that real-world usage of any drugs approved under accelerated approval are closely aligned with clinical-trial designs. "If a court develops a bad precedent, you don't continue the bad precedent. You revise the precedent," he says.

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