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News in focus

KAYANA SZYMCZAK/NYT/REDUX/EYEVINE

Dewayne Nash, a retired physician in Santa Barbara, California, took part in a trial of the Alzheimer's drug aducanumab.

LANDMARK ALZHEIMER'S DRUG APPROVAL CONFOUNDS RESEARCH COMMUNITY

Many scientists say there is not enough evidence that Biogen's aducanumab is an effective therapy for the disease.

By Asher Mullard

The US Food and Drug Administration (FDA) last week approved the first new drug for Alzheimer's disease in 18 years. The move was welcomed by some people looking for hope in treating an intractable condition. But, for many researchers, it came as a surprise – and a disappointment.

Aducanumab – developed by biotechnology company Biogen in Cambridge, Massachusetts – is the first approved drug that attempts to treat a possible cause of the neurodegenerative disease, rather than just the symptoms. But the approval has sparked a contentious debate over whether the drug is effective. Many experts, including an independent panel of neurologists and biostatisticians, advised the FDA that clinical-trial data did not conclusively demonstrate that aducanumab could slow cognitive decline.

The FDA instead relied on an alternative measure of activity, which sets a dangerous precedent, some researchers warn.

Current Alzheimer's drugs address only disease symptoms, for instance by delaying memory loss by a few months. Aducanumab clears out clumps of a protein in the brain called amyloid-β, which some researchers think is the root cause of Alzheimer's. This theory is known as the amyloid hypothesis. The FDA approved the drug on the basis of its ability to reduce the levels of these plaques in the brain.

"This is a very slender reed upon which to hang an approval decision," says Jason

Karlawish, a geriatrician and co-director of the Penn Memory Center in Philadelphia, Pennsylvania. Despite the dominance of the amyloid hypothesis over the past few decades, evidence that links reduction in plaque levels to improvements in cognition is "thin, at best", says Karlawish.

"Desperation should drive the funding of science, not drive the way we interpret the science," he says.

Desperate need

But some patient groups are desperate for anything that might offset the effects of the incurable, progressive disease. Estimates suggest that 35 million people worldwide have Alzheimer's.

"History has shown us that approvals of the first drug in a new category invigorate the field, increase investments in new treatments and encourage greater innovation," said Maria Carrillo, chief science officer for the patient-advocacy group Alzheimer's Association in Chicago, Illinois, in a statement. "We are hopeful, and this is the beginning — both for this drug and for better treatments for Alzheimer's."

Others worry that the approval will have the opposite effect — stymieing research efforts. Karlawish suspects that people with Alzheimer's might start dropping out of ongoing clinical trials to take aducanumab. Others worry that drug developers might abandon other targets. If demonstrating amyloid-lowering activity is enough to win regulatory approval, it might discourage developers from focusing on treatments with the big cognitive benefits that patients need, say some scientists.

"This is going to set the research community back 10–20 years," says George Perry, a neurobiologist at the University of Texas at San Antonio and a sceptic of the amyloid hypothesis.

'Problematic data set'

Aducanumab, an intravenously infused antibody, is the latest in a long line of therapeutic candidates that aims to tackle amyloid plaques. Every previous drug of this type has so far failed to improve cognition, and questions have persisted about whether amyloid-β is the right drug target, as well as whether researchers are testing the optimal therapeutic candidates, the correct doses and the appropriate patients.

"The problem with most of the amyloid trials is that they didn't disprove anything," says Bart De Strooper, director of the UK Dementia Research Institute in London. "They just proved that a drug, in the way it was applied, didn't work."

Researchers' concerns now centre on aducanumab's tumultuous passage through clinical trials and the resulting data set, which is incomplete and unpublished.

The FDA's approval is based on data from two phase III trials. In March 2019, researchers peeked at interim data while these trials — which were conducted in people with early-stage Alzheimer's — were ongoing. They concluded that these were unlikely to succeed, and Biogen halted both trials early.

But months later, the biotech firm brought the antibody back from the brink, after inspecting the data more closely. The slowing of cognitive decline was statistically significant in a subset of participants who received the highest dose of aducanumab, Biogen's re-analysis showed. Aducanumab did not have the same benefit when used at a lower dose in this trial, and it didn't show a benefit at any dose in the other trial.

For Paul Aisen, director of the University of Southern California's Alzheimer's Therapeutic Research Institute in San Diego, the totality of the data supports approval. "My personal view is that aducanumab is an effective therapy," says Aisen, who consults for Biogen. "But this was a problematic data set. It was a very fraught situation," he concedes.

These tensions were on display last November at an FDA meeting to discuss the trial data. An independent panel of experts advising the FDA evaluated the data and argued strongly against Biogen's assertion that the partial positive trial results carried more weight than did the negative ones. Scott Emerson, a biostatistician at the University of Washington in Seattle, who was on the panel, called the approach akin to "firing a shotgun at a barn and then painting a target around the bullet holes".

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The data also showed that aducanumab has non-negligible side effects. Around 40% of treated participants in the two trials developed brain swelling. Most people wouldn't have any symptoms related to the swelling, but they would need regular brain scans to avert dangerous complications — a burden for patients, neurologists and health-care systems.

At the November meeting, 10 out of 11 panellists ultimately voted that the presented data could not be considered as evidence of aducanumab's effectiveness; the remaining panellist was uncertain. Last week, the FDA reached the opposite conclusion.

Post-approval trial

As a condition of the FDA's approval — which relied on the agency's 'accelerated approval' programme — Biogen now must run a 'post-marketing' trial to confirm that the drug can improve cognition. It has yet to release details on when and how this trial will take place. Biogen has up to nine years to complete the trial.

This worries industry watchers. "Experience shows that relying on accelerated approval to gather timely, high-quality post-approval evidence is not necessarily a given," says Aaron Kesselheim, who studies pharmaco-economics at Harvard Medical School in Boston, Massachusetts, and is a member of the FDA panel that discussed aducanumab.

The FDA's choice to grant accelerated approval to aducanumab — after a roller-coaster of a clinical-trial programme — could have broader implications, too. "This opens the door to drug companies seeking to use the accelerated approval programme as a way of getting drugs on the market based on extremely low-quality evidence or post hoc data fishing," says Kesselheim.

Ripple effects

Biogen is now in line for a major windfall with aducanumab; its share price jumped by 40% on the approval.

Some experts had expected the FDA to approve the antibody only for people with early-stage disease, but the regulator has not limited its use — anyone with Alzheimer's can take it. Biogen will charge around US$56,000 per year per person for the drug. If 5% of 6 million people with Alzheimer's in the United States received the treatment, the drug's revenue would reach nearly $17 billion per year. This would make it the second top-selling drug, by current revenues.

The Institute for Clinical and Economic Review, a non-profit organization in Boston, Massachusetts, estimates that a cost-effective price is $2,500–8,300 per year.

The approval is also likely to shake up the development of future Alzheimer's drugs, say researchers.

With a pathway to approval established, drug developers are likely to double down on anti-amyloid drugs. Drug companies Eli Lilly, Roche and Eisai already have anti-amyloid antibodies in phase III trials. They, too, might now be able to secure approvals with evidence of amyloid-lowering activity, regardless of the compounds' effects on cognition.

Before the approval, the research community had started to shift towards other drug targets associated with Alzheimer's disease. For instance, more than ten drug candidates now in clinical trials are designed to clear the brain of another toxic protein, called tau.

David Knopman, a neurologist at Mayo Clinic in Rochester, Minnesota, hopes that these and earlier-stage efforts won't falter as a result of aducanumab's win, based on amyloid-lowering activity. "We need to look at other targets," he says.