# Aducanumab explained:
## history, controversies and opportunities

New Alzheimer's drug aducanumab has been hailed as a first-of-its kind treatment, generating global interest, but also controversy. **Emily Rosenich, Paul Maruff, Rachel Buckley** and **Yen Ying Lim** explain

In June this year the US Food and Drug Administration (FDA) approved a novel drug for the treatment of Alzheimer's disease – on the condition that further research trials show a clinical benefit of the drug. The drug, called Aduhelm (also known as aducanumab), is the first treatment approved for Alzheimer's disease in almost two decades, and the headlines were certainly hard to miss:

*"United States approves first Alzheimer's drug in 18 years, Biogen's aducanumab".*

*"If the FDA approves aducanumab, I won't prescribe it".*

*"Historic moment: US regulators approve landmark Alzheimer's drug".*

*"Bad medicine: aducanumab is a lacklustre drug with a high cost".*

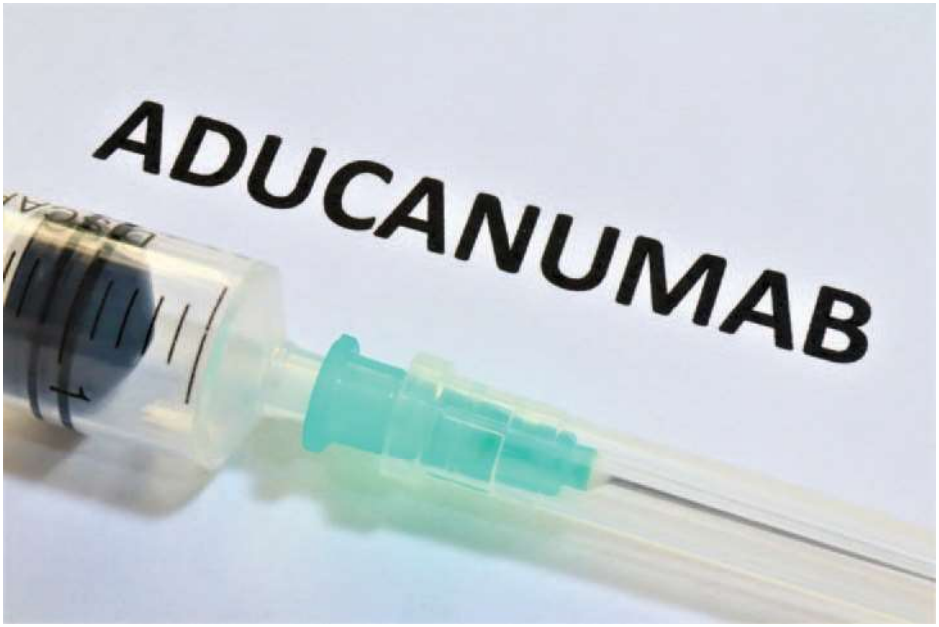
The FDA's approval of Aduhelm has been controversial amongst scientists, clinicians, not-for-profit organisations, and people living with dementia and their carers. The approval of Aduhelm is the first that the field has seen in recent decades, so why was this approval so controversial?

### What is Aduhelm?

Aduhelm, developed by Biogen, is marketed as the first disease-modifying treatment for early-stage Alzheimer's disease. At the moment, Aduhelm has been approved only in the US. Companies that develop drugs must provide evidence of their effectiveness to the government health authorities in each country in which they intend to make it available. This process has not yet been completed in Australia.

### Why is Aduhelm such a breakthrough?

All drugs that have previously been approved for use in the treatment of Alzheimer's disease (eg, donepezil) have been symptom modifiers. Symptom modifiers work by replacing brain chemicals or neurotransmitters that are lost as a consequence of brain cell death in Alzheimer's disease.




**The major controversy with the FDA's approval of Aduhelm (aducanumab) was that the clinical trials did not show convincing evidence that the drug slowed decline in memory and thinking**

Unfortunately, these drugs have a small beneficial effect on thinking and memory, and the beneficial effects do not last very long. This is because the root cause of cell death hasn't been treated, and any attempt to replace lost brain chemicals becomes ineffective as the disease becomes more severe.

Complex behaviours such as memory, thinking and conducting everyday activities are often underpinned by multiple brain pathways. Brain cell death in Alzheimer's disease often results in the loss of these pathways. Symptom modifier drugs typically only replace one type of brain chemical (ie, acetylcholine), which may be insufficient in overcoming the impairment in thinking, behaving, and feeling that arise from Alzheimer's disease-related cell death. This situation is summarised effectively with an analogy: "Imagine the damage caused by Alzheimer's disease in the brain is equivalent to a boat springing a leak. The drugs we currently have act to bail water out of the boat, but they don't do anything to plug the hole. Plugging the hole is the aim for disease modifying therapies" (Brain Health Scotland 2021).

Disease modifying drugs are designed to target the Alzheimer's disease processes that cause cell death. By stopping such processes, cells do not die and will continue to function normally, and brain chemicals will not be lost.

Aduhelm is a drug that is designed as a disease modifier, and Biogen has argued that data from its clinical trials suggests that it can plug the hole in the boat.

### How was Aduhelm tested?

Biogen conducted two large clinical trials (ENGAGE and EMERGE) (Biogen 2020). Each trial included over 1500 people with Alzheimer's disease. Both trials showed that Aduhelm successfully cleared amyloid from the brain. However, in 2019, Biogen announced that it was stopping both trials early, as its data showed that it was very unlikely the drug would have a positive effect on slowing memory loss.

A short while later, Biogen released a

statement saying that, upon analysing the final data alongside new data that wasn't previously available, Aduhelm did have a very small, albeit positive effect on thinking and memory and a person's ability to carry out day to day tasks. Importantly, this finding was only apparent in a subset of individuals: those who received the highest dose of the drug. From these findings, Biogen sought approval for use from the FDA in the US.

## Why was the approval of Aduhelm controversial?

The major controversy with the FDA's approval of Aduhelm was that the clinical trials did not show convincing evidence that the drug slowed decline in memory and thinking. Aduhelm does substantially reduce the amount of amyloid in the brains of people with Alzheimer's disease. Indeed, there are several drugs that can successfully remove amyloid from the brain.

However, in the world of drug development, the most important outcomes from clinical trials are how any new drug influences survival, or how it affects the way a person feels or functions. In trials of new drugs for Alzheimer's disease, this translates to how any drug can improve the ability of people to remember and think, as well as how it improves their ability to be able to live independently. With Aduhelm, these effects were quite small. Therefore, although the drug was effective in removing amyloid from the brain, this removal did not result in the improvements to the everyday life of participants.

The disconnect between drugs being able to remove amyloid but not improve symptoms is not unique to Aduhelm and has also been seen in other anti-amyloid drugs. This has raised two main questions. The first is whether the drugs are sufficiently effective. The second is whether removing amyloid is the right target if it has no impact on the clinical symptoms of Alzheimer's disease, such as memory loss. This speaks to a core debate within the field. Some scientists argue that disease progression in Alzheimer's disease refers to the biology of the disease (eg, the build-up of amyloid and tau) (Jack *et al* 2018). Others contend that disease progression should refer to the clinical symptoms of the disease (eg, memory loss), as this is what is meaningful to patients and their families.

## Why has it taken so long to develop Aduhelm?

Alzheimer's disease is a disease of time and can develop over 30 years. For a long time, scientists had only a limited understanding of this disease in humans.

While we knew that amyloid and tau proteins build up to abnormal levels in people who have died with Alzheimer's disease, there was no technology to study these abnormal proteins in humans who were alive.

One crucial development to understanding Alzheimer's disease and developing a drug to treat it was having the right tools. Brain imaging and brain fluid analysis have allowed us to measure amyloid and tau in living individuals, and to understand how these levels were related to age, genetics, and memory and thinking abilities (Rowe & Villemagne 2011). This was only made possible by conducting long-term studies of people with a family history of the disease. By studying them over time, we were able to identify demographic, genetic, and behavioural factors that increased a person's risk of amyloid and tau build up and decline in memory and thinking. This provided important insights into who and what to target.

Research now suggests that Alzheimer's disease begins with the build-up of amyloid in the brain, which results in the development of amyloid plaques (Jack *et al* 2018). As amyloid builds up, there is a consequent build up in tau. Currently, we think that it is this build-up in tau that leads to cell death and declines in thinking and memory. Some scientists refer to amyloid as the 'trigger', as once the trigger has been pulled, then the 'bullet' (tau) is on its way.

Thus, stopping the build-up of amyloid, or removing it, became a key strategy in the development of disease modifying drugs for Alzheimer's disease. The idea is that if we get rid of amyloid, this will stop tau from accumulating, which will mean that cell death will be prevented, and the thinking and memory that depend on these cells will be preserved. This is the theoretical basis of Aduhelm. Aduhelm works by breaking down the toxic build-up of amyloid protein in the brain.

## Why did the FDA approve Aduhelm?

When a company applies to the FDA to seek permission to market their drug, the doctors, scientists, and statisticians at the FDA pore over every detail of the clinical trial program. They examine everything from the original studies conducted in cells, in animals, and in humans. The company must provide the FDA with the raw data from their experiments and allow the FDA to analyse it independently to ensure that no errors have been made.

# The BetterBrains trial

It is currently estimated that about 40% of all dementias can be attributed to risk factors that are highly modifiable, including low mood, poor sleep, poor heart health and low cognitive and social engagement.

The BetterBrains trial, led by Australia's Monash University and the University of Melbourne, will test whether personalised lifestyle and educational behaviour change strategies targeted at modifying these four risk factors can prevent thinking and memory problems in middle-aged adults aged between 40 and 70 years.

The BetterBrains trial is unique, in that it is delivered fully remotely (ie, online, via telephone and smartphone application). The trial aims to recruit 1510 people living in the community throughout Australia. After completing an initial assessment, participants will be allocated at random (like tossing a coin) to one of two study groups. Of these people, 755 participants will be randomised to the intervention group and will receive the personalised BetterBrains program, while the other 755 participants will receive health education materials about dementia risk reduction.

To learn more about the BetterBrains trial, or to sign-up, visit www.betterbrains.org.au

### The Healthy Brain Project

Another Australian research initiative, The Healthy Brain Project, is also seeking volunteers – for a study to understand optimal brain health and ageing. To do this, neuroscientists at the Turner Institute for Brain and Mental Health, Monash University hope to gather a comprehensive amount of information from 10,000 volunteers and follow them each year for at least five years (or longer if possible) with the aim of identifying which parts of brain biology, genes, psychology and behaviour can help predict who will progress to develop dementia later in life. To volunteer or find out more, visit www.healthybrainproject.org.au

The process is incredibly detailed and thorough.

In addition to their own analyses, the FDA may seek advice from external experts in the field. These are often specialist doctors who treat the disease for which the drug is designed or other scientific experts who know the therapeutic area very well. This panel of independent experts will meet in a public forum, with the study sponsor (ie, Biogen) and the FDA to discuss the results of the studies that have been submitted for approval.

When assessing Biogen's proposal for FDA approval, 10 out of 11 experts on the expert advisory panel voted that the evidence for the therapeutic benefit of Aduhelm was inconclusive, and the remaining expert declined to vote. They recommended that Biogen's application for FDA approval of Aduhelm be rejected, based on the fact that they were asked to vote on the clinical efficacy of the drug (ie, benefit to memory and thinking ability, and ability to conduct everyday activities).

The FDA then integrated this opinion from the advisory board with its own consideration of the data provided by Biogen and approved Aduhelm.

It offered what was termed an 'accelerated approval', based not on the clinical efficacy, but on the evidence that the drug was effectively clearing amyloid plaques from the brain.

Consideration of the definition of an FDA accelerated approval helps to understand their decision. Under the Accelerated Approval pathway, the FDA may approve a drug for a serious or life-threatening illness that may provide meaningful therapeutic benefit over existing treatments when the drug is shown to have an effect on a surrogate endpoint that is reasonably likely to predict a clinical benefit to patients, despite there being some uncertainty about the drug's clinical benefit.

As Alzheimer's disease is considered in many developed countries to be a health emergency, the FDA required that Biogen continue to research the drug. It made Biogen commit to conduct another longer-term study and then come back to the FDA with those results. If this additional study fails to find a meaningful benefit, the approval will be withdrawn. Biogen is given almost a decade to provide data from this longer-term study (US Food & Drug Administration 2021b).

## What's next?

After nearly two decades of research, we now have the first disease-modifying drug for Alzheimer's disease. Aduhelm is effective in clearing amyloid from the brain. However, the benefits on memory and thinking have been small. Additionally, consequential side-effects, including brain swelling and haemorrhages, were reported in one out of three people taking the highest dose of the drug (US Food & Drug Administration 2021b).

We, like all Alzheimer's disease researchers and clinicians, sincerely hope that this drug is found to be effective when it moves into more widespread clinical use.

From a broader scientific perspective, an enormous step has been taken. We have now achieved a small but important beachhead in the war on this terrible disease.

While drug development in Alzheimer's disease has focused on amyloid, the field is increasingly turning its attention towards other drugs, such as those that target tau and neuroinflammation, or even multi-combination drug treatments.

The approval of Aduhelm will now accelerate the development and improvement of other drugs that modify biology to diminish cell death that devastates people and their families.

This achievement also re-energises researchers like us. It shows us that we are getting closer to the core of this disease. For us, the approval of Aduhelm is not the end of a project, it is the beginning of the next step. ■




From left: Dr Emily Rosenich is a Postdoctoral Research Fellow at the Turner Institute for Brain and Mental Health at Monash University; Professor Paul Maruff is a neuropsychologist and has a company, Cogstate, that works with pharmaceutical companies to help determine the benefits and risks of new drugs being developed for the treatment of dementia; Dr Rachel Buckley is a neuropsychologist based in Boston, US, as Faculty at Massachusetts General Hospital/Harvard Medical School; and Yen Ying Lim is an Associate Professor at the Turner Institute for Brain and Mental Health at Monash University. She is the primary investigator of the BetterBrains Trial and the Healthy Brain Project (see box p21).

**This article was originally published in Monash University's *Healthy Brain Newsletter* in July 2021. Republished here with the permission of the authors and The Healthy Brain Project, Turner Institute for Brain and Mental Health, Monash University**

**References**

ABC News (2021) *United States Approves First Alzheimer's Drug In 18 Years, Biogen's Aducanumab*. Available at: www.abc.net.au/news/2021-06-08/us-approves-first-alzheimers-drug-in-20-years/100197170. (Accessed 18/06/21).

Biogen (2020) EMERGE and ENGAGE Topline Results: Two Phase 3 Studies To Evaluate Aducanumab In Patients With Early Alzheimer's Disease. Available at: https://investors.biogen.com/static-files/8e58afa4-ba37-4250-9a78-2ecfb63b1dcb. (Accessed 18/06/21).

Brain Health Scotland (2021) *Aducanumab*. Available at: www.brainhealth.scot/aducanumab. (Accessed 18/06/21).

Jack Jr CR, Bennett DA *et al* (2018) NIA-AA Research Framework: Toward A Biological Definition of Alzheimer's Disease. *Alzheimer's & Dementia* 14(4) 535-562.

Maruff P (2016) *Alzheimer's Breakthrough? Have We Nearly Cured Dementia? Not Just Yet…* . Available at: https://theconversation.com/alzheimers-breakthrough-have-we-nearly-cured-dementianot-just-yet-62435. (Accessed 18/06/21).

Rowe CC, Villemagne VL (2011) Brain Amyloid Imaging. *Journal of Nuclear Imaging* 52(11) 1733-1740.

STAT News (2021) *If The FDA Approves Biogen's Alzheimer's Treatment, I Won't Prescribe It.* Available at: www.statnews.com/2021/05/30/if-the-fda-approves-biogens-alzheimers-treatment-i-wont-prescribe-it/. (Accessed 18/06/21).

STAT News (2021) *Bad Medicine: Aducanumab Is a Lacklustre Drug With A High Price Tag.* Available at: https://www.statnews.com/2021/06/08/aducanumab-lackluster-drug-high-price/. (Accessed 17/06/21).

The World News (2021) *Historic Moment: US Regulators Approve Landmark Alzheimer's Drug*. Available at: https://theworldnews.net/au-news/historic-moment-us-regulators-approve-landmark-alzheimer-s-drug. (Accessed 18/06/21).

US Food & Drug Administration (2021a) BLA Accelerated Approval. Available at: www.accessdata.fda.gov/drugsatfda_docs/appletter/2021/761178Orig1s000ltr.pdf. (Accessed 18/06/21).

US Food & Drug Administration (2021b) *Aduhelm: Full Prescribing Information.* Available at: www.accessdata.fda.gov/drugsatfda_docs/label/2021/761178s000lbl.pdf. (Accessed 18/06/21).