Title
Regulatory decisions diverge over aducanumab for Alzheimer’s disease

Authors
Lythgoe, Mark P
Jenei, Kristina
Prasad, Vinay

Publication Date
2022

DOI
10.1136/bmj-2021-069780

1Department of Surgery and Cancer, Imperial College London, London, UK
2School of Population and Public Health, University of British Columbia, Vancouver, British Columbia, Canada
3Department of Epidemiology and Biostatistics, University of California San Francisco, San Francisco, USA
Correspondence to: M P Lythgoe
M.Lythgoe@imperial.ac.uk

Cite this as: *BMJ* 2022;376:e069780
http://dx.doi.org/10.1136/bmj-2021-069780
Published: 28 January 2022

Regulatory decisions diverge over aducanumab for Alzheimer's disease

FDA's accelerated approval is a controversial outlier

Mark P Lythgoe, Kristina Jenei, Vinay Prasad

The European Medicines Agency refused marketing authorisation for aducanumab (Aduhelm), a monoclonal antibody targeted at amyloid β, in December 2021. It noted that "although Aduhelm reduces amyloid beta in the brain, the link between this effect and clinical improvement had not been established."[1] Furthermore, it concluded "studies did not show that the medicine was sufficiently safe," citing reported side effects including brain swelling and bleeding. This decision contrasts with that of the US Food and Drug Administration, which granted the drug accelerated approval in June 2021.[2]

The FDA's approval of aducanumab for treatment of Alzheimer's disease was based on a reduction in amyloid β plaques during clinical trials. Reduction in plaque levels is not a clinical endpoint, however, and the drug's manufacturer, Biogen, is required to complete post authorisation trials evaluating true clinical benefit.

This FDA approval has been one of the most consequential and controversial regulatory decisions in recent years.[3] The FDA's peripheral and central nervous system drugs advisory committee voted almost unanimously against approval, and three panellists resigned following the decision.[4 5] A reduction in amyloid β plaques is known to be an unreliable surrogate for cognitive improvement or delayed clinical decline in adults with dementia, leading to criticism of this endpoint to justify accelerated approval.[6 7] This has fuelled wider discussions about the use of accelerated approval more broadly.[8 -10] The FDA also allowed a generous nine years for confirmatory trials with clinical outcomes. Biogen has indicated these trials should be completed by 2026.[11] The FDA acting commissioner has called for an independent review of interactions between Biogen and FDA during the approval process, casting further doubt on the rigour and validity of authorisation.

The cost of treatment has also caused problems. Biogen announced an initial annual cost of $56 000 (£42 000; €50 000) per patient, over 10 times the price recommended by the independent Institute for Clinical and Economic Review.[12] When combined with a large, eligible population, this could lead to a big increase in Medicare expenditure. Although reimbursement decisions in the US usually follow FDA approvals, several leading healthcare providers and insurers have declined to use or fund aducanumab. In December 2021, Biogen announced a 50% reduction in the annual cost of aducanumab in the US after feedback from its stakeholders, in the belief that patients are not being offered aducanumab because of the substantial cost.[13]

The FDA and EMA have a high degree of concordance (>90%) in marketing authorisation decisions.[14] Although each agency evaluates applications independently, since 2003 dialogue and cooperation have expanded, fostering greater alignment in decisions. The divergence over aducanumab is therefore surprising, and it is important to consider possible reasons.

Different approaches

Typically, the FDA approves new drugs earlier than the EMA.[15] In the case of aducanumab, the EMA application was submitted 115 days after that to the FDA. This delay may have permitted an application with more mature clinical and safety data, including data from Biogen's phase III clinical trials showing that 41.3% of patients who received a high dose (10 mg/kg) of aducanumab experienced brain swelling or bleeding compared with 10.3% in the placebo group.[16] Furthermore, in 2018 the EMA adopted revised guidelines for the "clinical investigation of medicines for the treatment of Alzheimer's disease."[17,18] This guidance emphasises the need for clinical trials to show cognitive, functional, and global benefit. Authorisation of aducanumab would have been inconsistent with this recommendation.

New drug approvals require "substantial evidence" of efficacy, typically through a demonstration of how patients feel, function, or survive. Early approval pathways are intended to strike a careful balance to allow patients access to promising new therapies earlier, with confirmatory evidence later. FDA's accelerated approval pathway has permitted early access to transformative new therapies such as imatinib for chronic myelogenous leukaemia. However, in the early approval of aducanumab, the FDA is being overzealous, as the link between surrogate endpoint and improvement in symptoms or cognition has not been established, and is even refuted.[6 7]

The divergence in opinion between the EMA and FDA is significant and may reflect the EMA's more cautious and scientifically grounded approach to the accelerated pathways. Less than a week after the EMA decision, a Japanese health ministry advisory subgroup recommended deferring the decision on aducanumab, echoing similar efficacy and safety concerns and advising "effectiveness and safety should be re-examined through proper clinical trials."[19]

With Biogen intending to appeal the EMA verdict and multiple new anti-amyloid drug hopefuls (such as donanemab) nearing regulatory submission, the debate about this approval could shape neurodegenerative drug development for many

years.[11] Fostering greater engagement and harmonisation between global medicine regulators in their assessments would ensure regulatory standards and public trust are maintained.

Competing interests: *The BMJ* has judged that there are no disqualifying financial ties to commercial companies. The authors declare the following other interests: MPL has received advisory fees from Clovis Oncology; VP has received research funding from Arnold Ventures, royalties from Johns Hopkins Press and Medscape, honoraria for grand rounds or lectures from universities, medical centres, non-profits, and professional societies, consulting fees from UnitedHealthcare, and speaking fees from Evicore. His Plenary Session podcast has Patreon backers. Further details of *The BMJ* policy on financial interests are here: https://www.bmj.com/sites/default/files/attachments/resources/2016/03/16-current-bmj-education-coi-form.pdf.

Provenance and peer review: Not commissioned; externally peer reviewed.

1 European Medicines Agency. Refusal of the marketing authorisation for Aduhelm (aducanumab). 2021. https://www.ema.europa.eu/en/documents/smop-initial/refusal-marketing-authorisation-aduhelm-aducanumab_en.pdf
2 US FDA. Drugs@FDA: FDA-approved drugs. Aduhelm. https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=761178
3 Mullard A. FDA approval for Biogen's aducanumab sparks Alzheimer disease firestorm. *Nat Rev Drug Discov* 2021;20:496. doi: 10.1038/d41573-021-00099-3. pmid: 34112945
4 Mahase E. Three FDA advisory panel members resign over approval of Alzheimer's drug. *BMJ* 2021;373:n1503. doi: 10.1136/bmj.n1503. pmid: 34117086
5 Krudys KM. November 6, 2020 BLA 761178: peripheral and central nervous system drugs advisory committee meeting. Script for FDA presentation: aducanumab for the treatment of Alzheimer's disease: clinical overview of efficacy. https://www.fda.gov/media/143505/download
6 Ackley SF, Zimmerman SC, Brenowitz WD, etal. Effect of reductions in amyloid levels on cognitive change in randomized trials: instrumental variable meta-analysis. *BMJ* 2021;372:n156. doi: 10.1136/bmj.n156. pmid: 33632704
7 Panza F, Lozupone M, Logroscino G, Imbimbo BP. A critical appraisal of amyloid-β-targeting therapies for Alzheimer disease. *Nat Rev Neurol* 2019;15:73-88. doi: 10.1038/s41582-018-0116-6 pmid: 30610216
8 Lythgoe MP, Prasad V. How the US Food and Drug Administration's approval of aducanumab for Alzheimer's disease has implication for oncology and beyond. *Eur J Cancer* 2021;157:68-70. doi: 10.1016/j.ejca.2021.08.012. pmid: 34487987
9 Emanuel EJ. A middle ground for accelerated drug approval-lessons from aducanumab. *JAMA* 2021;326:1367-8. doi: 10.1001/jama.2021.14861. pmid: 34554184
10 Gyawali B, Ross JS, Kesselheim AS. Fulfilling the mandate of the US Food and Drug Administration's accelerated approval pathway: the need for reforms. *JAMA Intern Med* 2021;181:1275-6. doi: 10.1001/jamainternmed.2021.4604. pmid: 34254981
11 Biogen. Update on the phase 4 confirmatory study of Aduhelm. 16 Dec 2021. | https://investors.biogen.com/news-releases/news-release-details/update-phase-4-confirmatory-study-aduhelmr
12 Robinson JC. Why is Aducanumab priced at $56,000 per patient? Lessons for drug-pricing reform. *N Engl J Med* 2021;385:2017-9. doi: 10.1056/NEJMp2113679. pmid: 34797614
13 Biogen. Biogen announces reduced price for Aduhelm® to improve access for patients with early Alzheimer's disease. Press release, 20 Dec 2021. https://investors.biogen.com/news-releases/news-release-details/biogen-announces-reduced-price-aduhelmr-improve-access-patients
14 Kashoki M, Hanaizi Z, Yordanova S, etal. A comparison of EMA and FDA decisions for new drug marketing applications 2014-2016: concordance, discordance, and why. *Clin Pharmacol Ther* 2020;107:195-202. doi: 10.1002/cpt.1565. pmid: 31306483
15 Downing NS, Zhang AD, Ross JS. Regulatory review of new therapeutic agents—FDA versus EMA, 2011-2015. *N Engl J Med* 2017;376:1386-7. doi: 10.1056/NEJMc1700103. pmid: 28379798
16 Salloway S, Chalkias S, Barkhof F, etal. Amyloid-related imaging abnormalities in 2 phase 3 studies evaluating aducanumab in patients with early Alzheimer disease. *JAMA Neurol* 2022;79:13-21. doi: 10.1001/jamaneurol.2021.4161 pmid: 34807243
17 European Medicines Agency. Revised guideline on clinical studies for Alzheimer's disease medicines. https://www.ema.europa.eu/en/news/revised-guideline-clinical-studies-alzheimers-disease-medicines
18 Walsh S, Merrick R, Milne R, Brayne C. Aducanumab for Alzheimer's disease? *BMJ* 2021;374:n1682. doi: 10.1136/bmj.n1682. pmid: 34226181
19 Japan delays decision on whether to OK new Alzheimer's drug. *Japan Times* 2021 Dec 23. https://www.japantimes.co.jp/news/2021/12/23/national/science-health/alzheimers-drug-japan-approval-delay/