Can we learn lessons from the FDA's approval of aducanumab?

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On 7 June 2021, aducanumab was granted accelerated approval for the treatment of Alzheimer disease (AD) by the FDA on the basis of amyloid-lowering effects considered reasonably likely to confer clinical benefit. This decision makes aducanumab the first new drug to be approved for the treatment of AD since 2003 and the first drug to ever be approved for modification of the course of AD. Many have questioned how scientific evidence, expert advice and the best interests of patients and families were considered in the approval decision. In this article, we argue that prior to approval, the FDA and Biogen's shared interpretation of clinical trial data — that high-dose aducanumab was substantially clinically effective — avoided conventional scientific scrutiny, was prominently advanced by patient representative groups who had been major recipients of Biogen funds, and raised concerns that safeguards were insufficient to mitigate regulatory capture within the FDA. Here, we reflect on events leading to the FDA's decision on June 7, 2021 and consider whether any lessons can be learned for the field.

[H1] Introduction

As overall life expectancy increases globally, the number of older people living with dementia is projected to double every 20 years[1]. Alzheimer disease (AD), a slowly

progressive neurodegenerative disease that leads to cognitive and functional impairment, causes 60–80% of cases of dementia[2]. The defining histopathological lesions of AD neuropathological change — that is, parenchymal amyloid-β (Aβ) deposits, neuritic plaques and neurofibrillary tangles[3] — can appear decades before symptoms emerge and are associated with synapse loss, neuron loss, atrophy, gliosis and neuroinflammation. Although the sequence of events is not fully understood, the prevailing hypothesis that Aβ accumulation drives AD pathogenesis[4] has driven drug development in this field for nearly three decades. Cholinesterase inhibitors (donepezil, rivastigmine and galantamine) and memantine, available for the symptomatic treatment of AD since the late 1990s and early 2000s, have modest benefits and do not alter the underlying disease trajectory.

On June 7, 2021, the FDA granted accelerated approval **[G]** for aducanumab, a human recombinant anti-Aβ IgG1 monoclonal antibody and the first disease-modifying drug to be marketed for the treatment of AD[5]. Accelerated approval was based on evidence that aducanumab reduces levels of Aβ plaques in the brain, an unvalidated surrogate trial endpoint considered “reasonably likely” to predict clinical benefit[5]. In light of doubts concerning clinical effectiveness and the FDA and Biogen’s controversial interpretation of the phase III trial data[6–11], the 7 June announcement was accompanied by expressions of concern and disapproval. These expressions of concern included the resignations of three standing members of the FDA Peripheral and Central Nervous System (PCNS) Drugs Advisory Committee[12], which, 7 months earlier, had agreed almost unanimously that substantial evidence for clinical efficacy had not been established and expressed

uncertainty as to whether Aβ plaque reduction conferred cognitive improvement[13]. As the story of aducanumab, marketed as Aduhelm, continues to unfold, we reflect on events leading to the controversial FDA decision and consider whether any lessons can be learned for the field.

[H1] Aducanumab's rise, fall and resurrection

[H2] Phase I and Ib trial data

Aducanumab was developed by Neurimmune, a Swiss biotechnology company[14], which entered into a collaboration and license agreement with Biogen in 2007 for aducanumab's development and commercialization[15]. Following demonstration of dose-dependent reduction of brain Aβ in a transgenic mouse model of AD[14], Biogen commenced a phase I trial (study 101) of aducanumab in 2011[16], in which 53 participants with mild-to-moderate AD received a single intravenous ascending dose. The study, published in 2016, found that aducanumab showed acceptable safety[17].

In 2012, Biogen commenced a randomized, double-blind, placebo-controlled phase Ib trial, study 103 (PRIME)[18]. The aim of the study was to further investigate aducanumab's safety and tolerability at doses of 1, 3, 6 and 10mg/kg given once per month for 12 months; a secondary aim was to assess the effect of the drug on amyloid-PET measurements[14]. Participants (N=197) with prodromal or mild AD had amyloid pathology confirmed using ^{18}F-florbetapir PET. Amyloid-related imaging abnormalities (ARIA), that is, oedema (ARIA-E) and haemorrhages (ARIA-H), are established side-effects of amyloid-reducing antibodies and can be asymptomatic or associated with headache,

confusion, visual disturbances or gait difficulties[19]. Of participants who received the 10 mg/kg dose of aducanumab, 41% had ARIA-E (with a higher incidence in *APOE ε4* carriers) and 25% had both ARIA-E and ARIA-H. In contrast, no detectable ARIA-E with or without additional ARIA-H occurred in the group of participants who received placebo. A subsequent protocol amendment added a titration arm to the ongoing study. For 23 participants who were *APOE* ε4 carriers in the titration arm, aducanumab dose was gradually increased from 1 mg/kg to 10 mg/kg over 1 year, while eight *APOE* ε4 carriers received placebo. This gradual dose titration was associated with a lower incidence of ARIA-E (35% of participants, most of whom continued treatment) than fixed doses of 10mg/kg (55% of participants)[20].

Study 103 reported that aducanumab was associated with dose-dependent and time-dependent reductions in brain amyloid, with the greatest reductions observed in the group of participants receiving the highest dose (10 mg/kg). Efficacy endpoints were exploratory and showed a dose-related reduction in clinical decline, with differences of up to -1.08 on the Clinical Dementia Rating-Sum of Boxes (CDR-SB) and 1.9 on Mini-Mental State Examination (MMSE) in the group of participants receiving the 10 mg/kg dose compared with a pooled placebo group[21]. Notably, the occurrence of ARIA — which required repeated MRI assessments, dose interruptions and/or reductions, and would have potentially unblinded affected participants — was also dose-dependent. ARIA were detected in 5% of participants receiving placebo and 6%, 13%, 37% and 47% of participants receiving 1, 3, 6 and 10 mg/kg aducanumab, respectively.

[H2] Phase III trial data

Prior to the completion of the phase Ib study, two identically designed, randomized, double-blind, placebo-controlled phase III trials — studies 301 (ENGAGE)[22] and 302 (EMERGE)[23] — commenced in 2015. The aim of these studies was to compare the clinical efficacy of low (3mg/kg in *APOE* ε4 carriers or 6mg/kg in non-carriers) or high (initially 6mg/kg in *APOE* ε4 carriers or 10mg/kg in non-carriers) 4-weekly doses of aducanumab over 78 weeks with placebo. The primary outcome was change in CDR-SB from baseline at Week 78, and secondary endpoints were changes in MMSE, the 13-item Alzheimer's Disease-Cognitive Subscale (ADAS-Cog13) and the Alzheimer's Disease Cooperative Study-Activities of Daily Living-MCI (ADCS-ADL-MCI). In 2017, on the basis of final phase Ib ARIA data, the phase III trial protocols were amended (Protocol Version 4) to increase the high dose in *APOE ε4* carriers from 6mg/kg to 10mg/kg[21]. An earlier amendment of the protocols (Protocol Version 3) had also changed dose management following ARIA, such that after the resolution of mild-to-moderate symptomatic ARIA, participants resumed treatment at the same dose and continued titration to the target dose, instead of suspending dosing or resuming at a lower dose.

On 21 March 2019, Biogen announced the termination of the phase III aducanumab studies after prespecified futility criteria were met[24]. The prespecified interim analysis for futility was performed on data collected up to 26 December 2018, when approximately half of participants had completed the Week 78 primary efficacy outcomes assessment. The futility analysis used pooled data from both studies and showed that conditional power (that is, the probability of the final analysis showing statistical significance in favour

of aducanumab) for the CDR-SB was < 20%. Up to this point, aducanumab had disappointingly but unsurprisingly failed to meet phase III primary efficacy endpoints, joining a list of failed-at-phase III Aβ monoclonal antibodies, including bapineuzumab[25], gantenerumab[26,27], solanezumab[27,28] and crenezumab[29], along with other classes of anti-Aβ agents[30].

Biogen subsequently performed an intention-to-treat (ITT) analysis on a larger dataset collected up to 20 March 2019, as data collection had continued as per study protocols until the futility decision. This dataset comprised 66% of participants who would have had an opportunity to complete Week 78 assessments in study 301 — a total of 1,652 and a 12% increase on the number represented in the data collected up to December 2018. The dataset for the ITT analysis also included 60% of participants who would have had an opportunity to complete Week 78 assessments in study 302 — a total of 1,643 and 18% more than in December 2018. Study 302 was now presented as showing a 22% (increased from 18%) improvement, and study 301 a 2% (reduced from 15%) worsening, on the primary CDR-SB endpoint in the high-dose aducanumab group compared with placebo[21](Table 1). In a Type C meeting **[G]** on 14 June 2019, the FDA interpreted these data as an indication that the futility analysis using pooled data could be considered "flawed", as the two key assumptions on which it was based, (that is, that the treatment effect across both studies was similar and would not change over time), were invalid[21]. Using non-pooled futility analyses, as now requested by the FDA, the high-dose arm of study 302 would not have met futility criteria in December 2018[21].

In a subsequent Type C meeting on 21 October 2019, the FDA judged that the results of the terminated phase III studies, with >40% missing endpoint data, were valid and interpretable[21]. Study 302 was viewed as an "exceptionally persuasive"[21] single trial on the basis of statistically significant differences on the CDR-SB, MMSE, ADAS-Cog13 and ADCS-ADL-MCI favouring the group receiving high-dose aducanumab over the group receiving placebo (Table 1). In contrast, study 301 was viewed as a negative study, with no significant differences between the groups of participants receiving aducanumab and placebo on these endpoints (Table 1). Of the 1,029 phase III study participants who received the high dose of aducanumab, 35.2% developed ARIA-E (compared with 2.7% in the group that received placebo) and 19.1% developed ARIA-H (compared with 6.5% in the group that received placebo). Of the participants with ARIA, 10.0% had symptoms, the most common of which were headache (46.6%), confusion (14.6%) and dizziness (10.7%), as well as nausea (7.8%), fatigue (4.9%) and blurred vision (4.9%).

For AD trials that include participants with mild cognitive impairment, the FDA can consider a statistically significant change in a prespecified composite primary outcome (for example, CDR-SB) in one well-controlled trial, that is supported by confirmatory evidence, to represent substantial evidence of effectiveness[31]. The FDA and Biogen collaborated to conduct post-hoc exploratory analyses of the data to investigate whether baseline differences, or differences in dosing, incidence of ARIA or number of participants with rapidly progressing disease could explain the divergent findings between the groups receiving high-dose aducanumab in studies 301 and 302[21]. They concluded that study 301 was disproportionately affected by a higher number of participants with rapidly

progressing disease in the high-dose group (9 compared with 4–5 in the other treatment and placebo groups) and a lower degree of exposure to the highest dose of 10mg/kg (that is, lower cumulative doses in the high-dose group) than the cohort in study 302. They reported that treatment effects were more likely to be observed in subgroups of participants exposed to at least eight doses of high-dose aducanumab and after excluding participants with rapidly progressing disease. Thus, the results of study 301 were considered not to detract from those of the 'positive' study 302, which was viewed as independently representing substantial evidence of clinical efficacy. Further, the 10mg/kg fixed-dose arm of the much smaller (N=197), phase II study (study 103) was also considered to support the substantial evidence of effectiveness for high-dose aducanumab provided by study 302. Following this interpretation, the FDA advised Biogen that submission of a marketing application was a reasonable option[21].

[H1] FDA approval process

On 22 October 2019, Biogen announced their intention to pursue FDA regulatory approval for aducanumab on the basis of efficacy analyses performed on data collected up to 20 March 2019[32]. They reported that study 302 had met its primary endpoint and that data from a subset of participants who received high-dose aducanumab in study 301 were supportive of findings from study 302. Following two further meetings with the FDA in February and June 2020, Biogen submitted a Biologics License Application (BLA) for regulatory approval to market aducanumab on 7 July 2020.

Concerns regarding the statistical analyses presented by the FDA and Biogen were publicly raised at the PCNS Drugs Advisory Committee meeting on 6 November 2020. The briefing document prepared for the meeting[21] revealed a striking conflict between the FDA's in-house statistical review and the FDA and Biogen's jointly authored interpretation of the trial data. The FDA's statistical reviewers concluded that the data did not support substantial evidence of clinical efficacy. They highlighted the invalidity of discounting the negative results of study 301 and favouring exploratory analyses of the 10mg/kg versus pooled placebo arms in Study 103 that were not specified by the trial's per protocol randomization or analysis plans. The FDA's statistical reviewers also raised serious concerns regarding the validity of making the presumptions that study 302 was 'right' and study 301 was 'wrong' on the basis of post-hoc analyses of selected participant subgroups that involved non-randomized comparisons, and thus could not have been adequately placebo-controlled. In our opinion, the FDA and Biogen did not give equal consideration to the possibility that study 302 was a false positive and that the observed 'treatment effects' were a result of greater decline in the group receiving placebo, differences in enrolment and CDR-SB outcomes between geographic regions, or random over-representation of participants with slow disease progression in the treatment group. In addition, the FDA's statistical reviewers highlighted a number of inconsistencies in the data, for example, the group of participants who received one to seven doses of 10mg/kg aducanumab in study 301, with or without the inclusion of participants with rapidly progressing disease, showed a treatment effect numerically worse than zero exposure, which was inconsistent with the results of study 302 and did not support an exposure–response model. Another reported inconsistency was the lack of high-dose-related

treatment effects in *APOE* ε4 non-carriers, for whom degree of exposure to the 10mg/kg dose was not affected by the mid-study protocol amendment (Protocol Version 4). This observation does not support the FDA and Biogen's conclusion that the degree of exposure to 10mg/kg aducanumab affected treatment response. Although the FDA and Biogen concluded that functional unblinding resulting from ARIA did not introduce bias — as the primary outcome remained the same after excluding post-ARIA observations — the statistical reviewers stated that this potential bias in the data could not be ruled out.

After reviewing the phase III data, addressing inconsistencies and clarifying areas of concern, the 11-member PCNS Drugs Advisory Committee voted almost unanimously that substantial evidence for clinical efficacy had not been established (one voted 'uncertain')[13]. Despite stating to the PCNS Drugs Advisory Committee that brain Aβ was not being used as a surrogate marker for efficacy[33], the FDA subsequently approved aducanumab on 7 June 2021, on the basis that brain Aβ reduction was "reasonably likely" to confer clinical benefit[5]. The events surrounding the FDA approval of aducanumab are summarized in Fig 1.

[H1] Lessons learned

[H2] Early scrutiny of results is essential

Notably, only relative differences (that is, percentage) and not absolute differences between drug and placebo groups, were initially released in Biogen's October 2019 press release[6], obscuring the magnitude and potential clinical significance of the claimed treatment-associated differences and the variability of decline in the group receiving placebo. Selected topline results were later presented at the Clinical Trials on Alzheimer's

Disease (CTAD) conference on 5 December 2019, but audience questions were screened and could only be submitted electronically[34]. Consequently, up to the PCNS Drugs Advisory Committee meeting on 6 November 2020, Biogen could be perceived to have completely controlled the narrative by restricting availability and potential interpretation of phase III data, bypassing public scrutiny at scientific meetings and avoiding conventional journal peer-review.

By the time the PCNS Drugs Advisory Committee meeting took place, the dominant and misleading narrative that aducanumab conferred a 22% reduction in clinical decline in one of two trials had already generated hopeful anticipation in many patients and families, clinicians, campaigners and investors[35,36]. At the time of writing, we have seen the publication of the FDA's perspective and justification for aducanumab's approval in a peer-reviewed journal[37], but Biogen's aducanumab phase III trial data have not been published, only submitted and later withdrawn from *The Journal of the American Medical Association*[38]. The field needs to ask why this absence of published trial data was tolerated and should demand full release of data from future trials prior to submission for approval to increase transparency and accessibility of, and confidence in, a new drug's efficacy and safety data.

[H2] Minimum clinically important differences

A relevant issue raised at the PCNS Drugs Advisory Committee meeting[33] and more recently in our earlier article[10] is that, even if study 302 had been completed and analyzed as planned and could be viewed as a truly positive study, the -0.39 point treatment-related

difference in CDR-SB at 78 weeks for high-dose aducanumab did not reach what is considered to be a minimum clinically important difference (MCID). That is to say, this difference was less than a clinically meaningful response, which has been defined for the CDR-SB as -0.98 points in MCI and -1.63 points in mild AD[39]. This difference is also smaller than the effect of 10mg donepezil after 24–26 weeks of treatment (-0.53 points on CDR-SB)[40]. Indeed, data from a study by Jutten and colleagues (published this year) indicate that, in individuals with prodromal and mild AD, the 95% ranges of outcome differences resulting from natural heterogeneity in disease progression over 18 months (in the absence of any treatment effect) are broad, for example, -0.35 to 0.35 points on CDR-SB[41]. Most of the effect sizes in the aducanumab trials fall within this 95% range and Jutten et al. suggested that treatment responses of less than 0.5 points on CDR-SB cannot be reliably distinguished from variation in score owing to chance[41]. Of course, any effect larger than zero can be shown to be statistically significant with a large enough sample size, as statistical significance — that is, a p-value threshold — is the likelihood that any effect is attributable to chance and is not a measure of effect size[42]. MCIDs need to be incorporated into clinical trials and drug development guidance so that sponsors are motivated to power trials to detect clinically meaningful differences, and not just statistical significance for small and trivial effects on clinical outcomes.

[H2] False hope versus negativism

On its website, the FDA describes itself as a “science-led organization... [that] uses the best scientific and technological information available to make decisions through a deliberative process”[43]. The FDA Center for Drug Evaluation and Research (CDER) is

referred to as the “main consumer watchdog” in the US pharmaceutical system that evaluates new drugs before they can be sold. The website goes on to explain that the CDER “prevents quackery…”, “provides doctors and patients the information they need to use medicines wisely” and “ensures that drugs… work correctly and that their health benefits outweigh their known risks"[43].

Although there were a number of enthusiastic supporters of aducanumab’s approval[36], it has been controversial and understanding how the FDA has fulfilled its regulatory role has been hard. In approval documents made publicly available from 22 June 2021[44,45], the FDA conceded that the aducanumab trial data did not provide evidence of substantial effectiveness to support standard approval, but still viewed study 302 as a ‘positive’ trial that suggested potential clinical benefit. The FDA pivoted towards the accelerated approval pathway on the basis of substantial evidence that aducanumab treatment results in Aβ plaque reduction. This premise, that Aβ plaque reduction was reasonably likely to predict clinical benefit, did not seem to have undergone external scientific peer-review and was not supported by the views expressed by the PCNS Drugs Advisory Committee[33] and FDA statistical team[21,46] during the meeting on 6 November 2020. In addition, several studies published before[30,47] and since[27] the FDA decision on aducanumab have failed to show a convincing relationship between reduction of Aβ and clinical benefit.

The FDA argued that previous Aβ-targeting antibodies that did not show clinical benefit had failed to substantially reduce Aβ plaques[37], setting aducanumab apart. However, in our opinion, the reported correlations between Aβ reduction and clinical change for the

monoclonal antibodies that do significantly reduce Aβ plaques (r=0.104, p=0.309 for aducanumab study 302[46] and r=-0.09, p=0.244 for donanemab[48,49]) remain unconvincing. Such correlational data was not reported for lecanemab (BAN2401)[50] but the effect of reducing amyloid levels by 0.1 standardized uptake value ratio units (0.19 MMSE point improvement, 95% confidence interval (CI) -0.038–0.42) in the lecanemab study was similar to that of aducanumab in study 302 (0.18 MMSE point improvement, 95% CI [47])[47]. Similarly, a placebo-controlled study of ganterenumab, another Aβ-targeting monoclonal antibody, reduced Aβ plaques but conferred no cognitive benefits in symptomatic or asymptomatic participants diagnosed with dominantly-inherited AD after treatment for 4–7 years[27]. Another consideration is that, although PET can have high sensitivity and specificity for detecting or excluding the presence of Aβ plaques[51,52], the accuracy of this technique for measuring longitudinal changes in Aβ plaque load is less clear[53,54]. In contrast to the questions over potential clinical benefit, the adverse effects of high-dose aducanumab are known and included either ARIA-E or ARIA-H in 43% of participants, one in four of whom (or 10% of the high-dose population) were symptomatic[21]. As a condition of accelerated approval, Biogen is required to conduct a post-marketing trial to verify the anticipated clinical effect within nine years[55]. However, this trial is unlikely to provide clarity on the issue, as previous post-marketing trials that showed positive outcomes for drugs that had received accelerated approval continued to use surrogate measures rather than clinical outcomes[56], if they were published at all[57].

AD leads to irreversible cognitive and functional decline. The FDA has emphasized that patients and their families are willing to accept the uncertainty and risks associated with

aducanumab treatment in exchange for earlier access to a potentially effective drug[37] and some in the scientific community believe this will provide patients with choice and the power to make their own health decisions[36]. An alternative view, however, is that a misleading narrative based on misinterpreted data will expose desperate and vulnerable patients with AD and their families to a treatment with no discernable clinical benefit and serious, potentially life-changing adverse effects. In light of serious concerns regarding the statistical validity of viewing study 302 as a 'positive' trial representing clinical efficacy, and major scientific limitations of using Aβ as a surrogate marker for clinical efficacy, patients and families should instead have been asked solely whether they would be willing to accept the risks for earlier access to a drug that reduced levels of a biomarker, even if a relationship between biomarker changes and clinical outcomes has not yet been established.

[H2] Specificity of indication

Surprisingly, the FDA initially approved aducanumab for the treatment of AD without specifying disease severity thresholds, amyloid-PET status, or contraindications[58]. Then, on 7 July 2021, the FDA approved an updated label, which specified that Aduhelm treatment should be initiated in individuals with MCI or mild dementia due to AD[59]. However, safety and efficacy data, on which approval was based, only apply to patients who would have met the aducanumab study inclusion criteria, which included amyloid -PET positivity and the absence of a high risk of abnormal bleeding (participants with bleeding disorders or those taking anticoagulant medications were excluded)[22,23]. Although clinicians will exercise clinical judgement and some expert guidance has now

emerged[60], the updated labelling still risks the potential unsafe and inappropriate use of aducanumab, for example, in individuals who have been misdiagnosed and do not have MCI or dementia due to AD. Up to 30% of cognitively normal older individuals have detectable brain amyloid using PET[61], and a proportion (at least 20–30%) of individuals with MCI who have levels of CSF or PET amyloid consistent with AD will not progress to dementia within 3 years[62,63]. The conversion rate is even lower for individuals who are amyloid positive but negative for CSF phosphorylated tau or total tau[62]. Therefore, it is possible that some individuals with positive amyloid-PET results do not have and will never develop a neurodegenerative disease[64]. How many doses of aducanumab are needed and when to stop treatment also remains unclear.

[H2] The potential for regulatory capture

Given the observed mismatch between the FDA's actions and their ascribed regulatory role, factors that may have influenced aducanumab's accelerated approval have been the subject of speculation and criticism. Although early engagement between the FDA and sponsors is officially encouraged[31,65], there has been concern that the unprecedented apparent closeness of the FDA and Biogen during[66], and even preceding[67], the submission process could represent a degree of regulatory capture. Recognizing the harm these claims pose to its integrity and reputation, on 9 July 2021, the FDA requested an independent investigation of alleged close links between the FDA and Biogen during the process that led to aducanumab's approval [68].

A broader concern is that the FDA has inadvertently been co-opted to serve the interests of special groups over the general interest of the public[69,70]. Legislative changes intended to speed up the approval process, such as the Prescription Drug User Fee Act (PDUFA) in 1992 and the 21st Century Cures Act in 2016, have potentially increased the FDA's reliance on industry funding, undermined its regulatory independence[71] and weakened regulatory standards. Some patient groups, such as Alzheimer's Association and UsAgainstAlzheimer's, also lobbied for the approval of aducanumab[72,73]. However, these groups have received substantial financial donations and sponsorship from Biogen over recent years. Although these potential conflicts of interest were declared elsewhere[74–78], they were not made explicit in the lobbying letters submitted to the FDA[72,73]. Mitigating the severity of future regulatory capture might be possible through a better understanding of its nature and the adoption of sufficient strategies to safeguard the objectives of regulation[70], for example, by incorporating greater sharing of decision-making power, increasing public transparency (for example, by publishing transcripts or audio recordings of regulator–sponsor interactions) and regularly reviewing the regulator's conflict of interest policies[79].

[H1] Conclusions: the era of aducanumab

The FDA suggests that aducanumab's accelerated approval "can bring therapies to patients faster while spurring more research and innovation"[80]. Indeed, the FDA and Biogen have provided a roadmap for manufacturers of other drugs with marginal or uncertain clinical benefit to successfully achieve marketing approval. Only a few weeks after aducanumab's approval, the FDA granted breakthrough therapy designation **[G]** to

two other Aβ-reducing monoclonal antibodies — donanemab and lecanemab — on the basis of phase II trial data[81,82], and Eli Lilly and Company announced their intention to seek accelerated approval for donanemab[82]. Other agents for which accelerated approval will now be sought could include anti-Aβ agents, for example, gantenerumab, that were previously shelved after accepted conventional analyses of phase III trial data did not indicate clinical efficacy. The approval of aducanumab might also hamper ongoing trials of AD drugs, as participants might drop out of trials to receive aducanumab as opposed to taking unapproved experimental drugs or risking allocation to placebo. Some researchers have argued that anti-Aβ drugs might not show disease-modifying effects in therapeutic clinical trials because they could be ineffective by the time a patient is symptomatic[83]. However, in our opinion, focusing on AD biomarkers and ignoring AD clinical phenotypes is problematic, as evidence indicates that a purely biological definition of AD has low predictive accuracy[64].

We need only to look at the cancer research field to understand the implications of aducanumab's accelerated approval for future AD drug treatments. To fulfill 'unmet medical need', the FDA granted accelerated approval for a number of cancer drugs over the past three decades on the basis of unvalidated surrogate markers[84,85]. The results of a study published in 2019 showed that only 20% of subsequent confirmatory trials of these cancer drugs demonstrated treatment-associated improvements in overall patient survival[86]. For now, the consideration of benefits versus risks in deciding whether to receive, prescribe or provide aducanumab shifts onto individual patients and their families, clinicians, health providers and insurance companies, who will also need to

consider the costs. Aduhelm is priced at $56,000 per year[87], not including the costs of clinical reviews and monitoring MRI scans, which will increase the financial burden on individuals and health care delivery systems. Under the US Medicare payment system, doctors currently receive commission (6%) on medications they administer[88], which might incentivize the prescription of more expensive drugs and create a conflict of interest.

The impact of financial toxicity, defined as the adverse economic consequences of medical diagnosis and treatment, on quality of life, morbidity and mortality, has been well-documented in patients with cancer[89,90] and might in future affect patients with AD and their families. The insurance coverage of drugs granted accelerated approval can be regulated by further assessment of clinical and cost effectiveness, and conditional coverage based on price concessions, collection of additional clinical outcome data, or restriction to specific patient subgroups[91]. However, these options are not yet available to US public health insurance programs, which are mandated to cover almost all FDA-approved drugs[92]. The FDA's reputation has undoubtedly been tarnished by aducanumab's approval. A number of private medical insurance companies have announced that they will not cover Aduhelm owing to lack of clinical benefit[93], the Institute for Clinical and Economic Review (ICER) has decided that there is insufficient evidence to conclude that any benefits of Aduhelm treatment outweigh the risks[94], and high-profile treatment centres such as the Cleveland Clinic and Mount Sinai have announced that they will not be offering Aduhelm to their patients until the controversy and doubt around efficacy and the circumstances of FDA approval have been resolved[95].

Overall, sponsors will have learned that a near-unanimous PCNS Drugs Advisory Committee vote against approval, (at best) uncertain evidence of clinical benefit derived from incomplete trial data and non-randomized comparisons, the presence of real risks and costs of treatment, and inadequate evidence for any clinical benefits of brain amyloid reduction were not sufficient reasons for the FDA to turn down marketing approval for aducanumab. In our opinion, Biogen were allowed to control the narrative of data presentation from an early stage by the organizers and attendees of scientific conferences, they avoided peer-review scrutiny of their data, and they potentially benefited from strategic donations and insufficient safeguards to mitigate regulatory capture[96]. The audacity of Biogen's conduct throughout this process has never been effectively challenged or checked by dementia scientists or those who speak for people with dementia, despite serious concerns that were expressed by a vocal minority. We have been surprised to learn that the FDA, despite claims to be a "science-led"[43] and "consumer watchdog"[43] regulatory body, ultimately does not seem to make decisions on the basis of scientific evidence, expertise, or in the objective interests of patients and families. However, in many ways, the whole dementia field bears responsibility along with the FDA for what might happen next.

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Author contributions

K. Y. L. researched data for the article, made a substantial contribution to discussion of content, wrote the article, and reviewed and edited the manuscript before submission. R. H. researched data for the article, made a substantial contribution to discussion of content, and reviewed and edited the manuscript before submission.

Competing interests

The authors declare no competing interests.

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Publisher's note

Table 1 | Phase III trial endpoints for aducanumab in the intention-to-treat population up to 20 March 2019

Assessment instrument	Change from baseline at Week 78			Difference from placebo (%)	
	Placebo	Aducanumab low-dose	Aducanumab high-dose	Aducanumab low-dose	Aducanumab high-dose
Study 301 (N=1,647[a])					
CDR-SB (N=959)	1.56	1.38	1.59	-0.18 (-12%); p=0.2250	0.03 (2%); p=0.8330
MMSE (N=963)	-3.5	-3.3	-3.6	0.2 (-6%); p=0.4795	-0.1 (3%); p=0.8106
ADAS-Cog 13 (N=957)	5.14	4.56	4.55	-0.58 (-11%); p=0.2536	-0.59 (-11%); p=0.2578
ADCS-ADL-MCI (N=959)	-3.8	-3.1	-3.1	0.7 (-18%); p=0.1225	0.7 (-18%); p=0.1506
Study 302 (N=1,638[a])					
CDR-SB (N=877)	1.74	1.47	1.35	-0.26 (-15%); p=0.0901	-0.39 (-22%); p=0.0120
MMSE (N=880)	-3.3	-3.3	-2.7	-0.1 (3%); p=0.7578	0.6 (-18%); p=0.0493
ADAS-Cog 13 (N=879)	5.16	4.46	3.76	-0.70 (-14%); p=0.1962	-1.40 (-27%); p=0.0097
ADCS-ADL-MCI (N=864)	-4.3	-3.5	-2.5	0.7 (-16%); p=0.1515	1.7 (-40%); p=0.0006

[a.]The planned sample size (originally N=1,350 in each study, which was increased to N=1,605 after a prespecified sample size reassessment in November 2017) was intended to provide ~90% power to detect a true mean difference of 0.5 points in change from baseline CDR-SB at Week 78 (the primary endpoint) between the two treatment groups. However, although Studies 301 and 302 enrolled N=1,647 and N=1,638 participants respectively, they had over 40% missing data at Week 78 due to early termination for futility in March 2019. CDR-SB, Clinical Dementia Rating-Sum of Boxes; MMSE, Mini-Mental State Examination; ADAS-Cog 13, 13-item Alzheimer's

Disease-Cognitive Subscale; ADCS-ADL-MCI, Alzheimer's Disease Cooperative Study-Activities of Daily Living-MCI.

Figure 1 | Timeline of events surrounding the FDA approval of aducanumab.

This timeline shows the series of events leading up to and following the accelerated approval of aducanumb by the FDA on 7 June 2021. [a] Originally reported by STAT[67]. [b] A Type C meeting is a formal meeting between the FDA and sponsor concerning the development and review of a product that does not fall within the scope of Types A (a necessary meeting for an otherwise stalled product development program to proceed or to address an important safety issue) or B (milestone meetings, such as end-of-phase I or II meetings) meetings.

Glossary

Accelerated approval: An FDA-instituted program to allow drugs that treat serious conditions and that fill an unmet medical need to receive earlier approval on the basis of a surrogate endpoint considered reasonably likely to predict a clinical benefit.

Type C meeting: A formal meeting between the FDA and sponsor concerning the development and review of a product that does not fall within the scope of Types A (a meeting necessary for an otherwise stalled product development program to proceed or to address an important safety issue) or B (milestone meetings, such as end-of-phase I or II meetings) meetings.

Breakthrough therapy designation: A process designed to expedite the development and review of drugs intended to treat a serious condition when preliminary clinical evidence

indicates that the drug might represent a substantial improvement over available therapies on a clinically significant endpoint or endpoints, which can be a surrogate endpoint considered reasonably likely to predict a clinical benefit.