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BIG PHARMA

Donanemab: Conflicts of interest found in FDA committee that approved new Alzheimer's drug

A new drug for Alzheimer's disease is causing excitement despite excess deaths, missing safety data, questionable efficacy, and financial conflicts of interest among the "independent" advisory panellists who recommended approval. Jeanne Lenzer and Shannon Brownlee report

Jeanne Lenzer, Shannon Brownlee

Donanemab (marketed in the US as Kisunla) was developed by Eli Lilly and approved by the US Food and Drug Administration (FDA) on 2 July. It is the latest in a new class of treatments for Alzheimer's disease that has been much praised in the media as "breakthrough drugs" and the first "disease modifying therapies" for the condition. All drugs in the class deliver antibodies that target β amyloid, a protein believed to cause the disease, and they share similar benefits and harms.

Their effectiveness, however, has been questioned. George Perry, editor in chief of the *Journal of Alzheimer's Disease*, told *The BMJ* that the new anti-amyloid drugs, such as aducanumab and lecanemab, "all demonstrate an imperceptible slowing of dementia in the midst of serious adverse effects, including death."

Donanemab, like the two previously approved Alzheimer's drugs, faces questions not only about its efficacy and the number of deaths among patients taking the drug but also about financial ties to drug makers among FDA advisory committee members. *The BMJ* has found that three advisers who recommended approval of donanemab received direct payments or research funding from its manufacturer, Lilly.

Deaths and adverse events

In January 2023 the FDA sent a letter to Lilly denying approval of donanemab.[1] In a briefing document the agency cited a "high rate" of missing data and concluded that the "safety database was insufficient to adequately characterize the long-term safety" of the drug.[2]

The FDA noted that treatment discontinuation because of adverse events was more common among patients taking donanemab than in the placebo group in Lilly's phase 3 trial. Patients who discontinued treatment were often withdrawn by researchers from the study and excluded from the final analysis.[3] This led to "incomplete vital status information," said the FDA, meaning the Lilly trial investigators didn't know whether a substantial number of test participants were dead or alive.[2]

Brain haemorrhage and swelling, collectively referred to as amyloid related imaging abnormalities (ARIA), occurred in 36.8% of patients taking donanemab and 14.9% of placebo patients. Along with infusion reactions, ARIA was the most frequent adverse event leading to treatment discontinuation. Lilly acknowledged three deaths in patients taking donanemab due to ARIA, which the investigators attributed to the drug.[3]

The FDA also noted interim data showing an "imbalance" in overall deaths: 17 (2.7%) in the group of patients taking donanemab and 10 (1.4%) in the placebo group.[2] In light of these findings, the agency told Lilly that the company would need to retrieve additional mortality information on the missing patients.

In response, Lilly hired an outside company to search "publicly available records and databases, social media, and traditional media" to obtain the missing data.[2] Lilly told *The BMJ* that data tracking was limited to sites that agreed to follow up and to countries where it's "legally permissible" to seek out patients through public media. Four of the eight countries refused: Japan, Netherlands, the Czech Republic, and Poland.

The outside company found 118 of the 221 (53%) missing patients in the donanemab arm and 66 of the 170 (39%) in the placebo arm.[2] Lilly declined to identify the name of the third party and its methods, telling *The BMJ*, "We do not disclose the names of our third party vendors." The hired company found two additional deaths among patients in the donanemab arm and five more deaths in the placebo arm. According to the FDA, that narrowed the "imbalance in deaths" to 19 in the donanemab arm and 15 in the placebo arm.[2]

Steven Goodman, a physician and professor of epidemiology at Stanford University, says it is not possible to assess the reliability of the new data without more details of the outside company's methods. "There was also no information on health outcomes in those patients other than death, or the causes of the deaths," he tells *The BMJ*, adding that the "failure to formally follow patients who stopped treatment was a significant design flaw, particularly when that discontinuation was partly due to adverse drug effects."

Because of safety concerns the FDA is requiring Lilly to conduct a post-market "registry based, prospective, observational study" to track events, including deaths, brain haemorrhage, and oedema. It is giving the company 13 years (until February 2037) to issue

its final safety report. Lilly must submit biannual reports to the FDA.[4]

Diana Zuckerman, president of the National Center for Health Research in Washington, DC, tells *The BMJ*, "Relying only on registry data and giving Lilly until 2037 is unacceptable. It shows indifference to the needs of patients and their families despite clear concerns about the potential increase in irreparable harm and deaths that would be evident after just a few years."

Besides the concerns over ARIA and deaths in the trials, experts have said that drugs such as donanemab might be worsening neurodegeneration (box 1).

Box 1: Brain shrinkage concerns

All drugs approved by the FDA in the same class as donanemab (anti-amyloid monoclonal antibodies) significantly accelerate brain shrinkage beyond the atrophy associated with underlying Alzheimer's disease.[5] Since progression of atrophy in Alzheimer's is associated with worsening cognitive function, a controversy has arisen over the implications of the drugs' effects.

Manufacturers claim that atrophy is evidence of a positive therapeutic effect as a result of reduction of amyloid and associated inflammation. However, one clue that medication induced atrophy might be speeding cognitive loss is the finding that in Lilly's phase 3 trial neurofilament light (NfL), a protein that increases with brain cell death, was higher in the donanemab arm than in the placebo arm at weeks 12 and 24 and fell off by week 76, according to the FDA.[2]

Last May, Madhav Thambisetty, then a senior investigator with the National Institutes of Health's National Institute on Aging (he is now at Novartis), told *The BMJ* that NfL levels might be expected to decrease if the drugs were slowing neurodegeneration. Without strong evidence to the contrary, he said, brain shrinkage in the presence of increased NfL indicated that the drugs could be worsening neurodegeneration and cognitive loss.

Conflicts of interest

FDA's approval of donanemab comes after its contentious approval of aducanumab (Biogen and Eisai's Aduhelm),[6] despite a unanimous vote against it by the agency's advisory committee (with one abstention). The advisers, many of whom were independent academics, objected to the agency's decision to allow the company to switch its endpoint to a surrogate (reduced amyloid) rather than the clinical endpoint, which was measured in its studies but had not shown a clear cut benefit.[7] Three advisers quit in protest, and a firestorm ensued in the press.[8] A Congressional investigation followed, finding the FDA's approval process to be "rife with irregularities."[9]

The second drug in the class, lecanemab (Eisai and Biogen's Leqembi), came up for review in 2023. By then the FDA had replaced all 11 members of its advisory committee who had been critical of aducanumab. The agency appointed four new physicians to the committee to review lecanemab; all of them, or their employers, had had financial ties from 2017 through to the end of 2023 to the manufacturers of lecanemab. No public data on financial ties were available for two additional advisers, a biostatistician and patient representative.

The new and much smaller six member committee approved lecanemab unanimously, and the FDA gave its nod to the drug in July 2023.

When donanemab came up for review earlier this year, the FDA expanded its advisory committee to 11 members, including eight physicians. Using the public database OpenPayments, members' CVs, disclosures in published articles, and the Google patent ownership database, *The BMJ* found that individual advisers received up to $62 000 (£47 000; €56 000) for consulting and speaking fees and up to $10.5m in research grants from 2017 through to the end of 2023 (table 1).

Table 1 | Financial ties of FDA advisory committee members found by *The BMJ* through publicly available databases

Name	Affiliation	Relevant financial interests*
Thomas Montine (committee chair)	Professor of pathology, Stanford University	Biogen ($1500); Avid Radiopharmaceuticals ($3941), a Lilly owned company that makes florbetapir, used to detect amyloid on PET scans; Genentech ($1500) and Roche ($115)—both these companies develop blood or urine tests for amyloid
Cynthia Carlsson	Geriatrician, William S Middleton Memorial Veterans Hospital, Madison, Wisconsin	Waiver granted†: Lilly ($1.8m in associated research funding) and Eisai ($592 570 associated research)
Merit Cudkowicz	Professor of neurology, Harvard Medical School	Lilly ($21 807 consulting fees and $2887 in research payments); Biogen ($40 256 consulting fees)
Nilufer Ertekin-Taner	Professor of neurology and of neuroscience, Mayo Clinic, Jacksonville, Florida	Holds one or more patents on use of naturally occurring monoclonal antibodies against amyloid β
Dean Follmann	Biostatistician, NIH, NIAID	No relevant interests found
Costantino Iadecola	Professor of neurology, Weill Cornell Medicine, New York	Biogen ($4200 consulting fees); has a patent for gene therapy to treat Alzheimer's disease
Colette Johnston (patient representative)		No data
Kathleen Poston	Professor in neurology, Stanford University	Sanofi ($1448 consulting fees)—Sanofi is developing antibodies to treat ARIA; Roche ($115 general payment)—Roche is developing blood test for amyloid. Received undisclosed amount for research support from the Alzheimer's Drug Discovery Foundation, which has received funding from Eli Lilly. Has "ownership interest" in biotech company Amprion and served on its board. Amprion develops diagnostic tests related to amyloid and Alzheimer's
Daniel Press	Professor in neurology, Stanford University	Waiver granted†: Biogen ($1.8m); Janssen ($170 869) and Novartis ($84 630)—both companies develop antibodies to treat Alzheimer's
Tanya (Tatyana) Simuni	Professor of neurology, Feinberg School of Medicine, Northwestern University	Biogen ($10.5m associated research); Lilly ($1250 consulting); Lilly/Hoffman LaRoche ($37 538 research and $6941 consulting)—joint endeavour for Alzheimer's diagnosis; direct consulting payments from makers of anti-amyloid drugs Genentech ($3600) and Takeda ($3675)
Sarah Zenner-Dolan (consumer representative)	Consultant, Critical Path Institute (C-Path)	C-Path is a public-private partnership with the FDA. Its CPAD (Critical Path for Alzheimer's Disease) division "works to speed up the development of Alzheimer's disease drugs," and its "strategic partners" are Biogen, Eisai, and Lilly, among others

General payments go directly to researchers for consulting and speaking fees or other services, while research funding is generally routed through the researcher's institution. However, drug industry funding has been repeatedly identified as a source of bias,[10] and payments of as little as $15 have been shown to affect attitudes of doctors towards a drug.[11]

* "Financial interests" lists details on the funding payments and any related financial ties with industry, as confirmed with the committee members, though three of the 11 (Montine, Simuni, and Johnston) did not respond to queries.

† "Waiver granted" indicates that the FDA granted a waiver to allow them to serve on the committee despite their declared financial conflicts.

In addition to the three physician advisers who had financial ties to Lilly, two had ties to Roche, Lilly's development partner in creating a new blood test for Alzheimer's disease.[12] Two other doctors have patents on amyloid antibodies, and the eighth doctor had research funding from Janssen for another Alzheimer's drug. Such financial conflicts are relevant because the failure of one drug in a class resulting from their shared mechanism of action (removal of amyloid, for example) can put all drugs and tests in the class at risk of being rejected by regulators.[13]

Federal law on conflicts of interest prohibits advisory members from having ties to companies that would have a "direct and predictable effect on the financial interests of the [adviser] or his employer."[14] The FDA asks prospective members to declare past financial interests and "anything that would give an 'appearance' of a conflict," without specifying a timeframe.[15] However, the agency can grant waivers if the prospective adviser's expertise is needed and outweighs potential bias. The agency granted a waiver to two of the advisory members who were seated.

Asked about the extensive financial conflicts among the physician advisers found by *The BMJ*, the agency stated, "The FDA does not comment on matters related to individual members of an advisory committee."

Efficacy in question

The primary endpoint of the donanemab studies was scores on the integrated Alzheimer's disease rating scale (iADRS), a 144 point composite scale of cognition and activities of daily living. The test was created by Lilly in 2015.[2] The FDA objected to Lilly's use of its own test and wanted the company to use the more widely accepted "clinical dementia rating scale—sum of boxes" (CDR-SB) test. The agency said that the company "changed the primary endpoint [from CDR-SB] to the iADRS during the conduct of the study," adding that "the agency did not agree with the change."[2]

In 2021 Lilly reported that its phase 2 trial "failed to show a significant difference" between patients taking the drug and placebo with respect to the CDR-SB score, which the FDA had urged Lilly to use as the primary outcome.[16 17] Lilly instead reported a 3.2 point difference on its iADRS score as the primary outcome. The 3.2 difference fell far below the level of a clinically meaningful difference, which according to Lilly's iADRS criteria would require a difference of at least 5 points.[18]

The subsequent phase 3 trial found an even smaller effect: a 2.92 difference on the iADRS.[3] This time the secondary endpoint, the CDR-SB, did reach a statistically significant difference of 0.7. However, that result also failed to reach the lowest threshold for a clinically meaningful effect of 1 to 1.6 points, as established by Lilly in 2019 from studies of 35 000 patients.[19] Anything less is not considered to be perceptible to patients or their carers.

Patients in the donanemab arm worsened on the iADRS by 10.2 points, while patients on placebo worsened by 13.1 points. That gives an absolute difference of 2.9 points or a relative difference of 22% between the two scores.

When it published the phase 3 results Lilly stated that donanemab slowed progression by 22%. Using subgroup analyses and relative rather than absolute values, the company has also promoted donanemab as "slowing decline by 35%."[20 21]

"That is a misleading statement," says Alberto J Espay, a neurologist and specialist in clinical epidemiology and healthcare research at the University of Cincinnati. "That's a relative difference that transforms a very tiny absolute difference into a number that seems impressive."

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