

Editorial

The FDA Approves Aducanumab for Alzheimer's Disease, Raising Important Scientific Questions¹

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One of the most jaw-dropping reversals of guidance procedures in the history of the Food and Drug Administration (FDA) took place last June 7, when the agency announced that the drug aducanumab, a monoclonal antibody manufactured by Biogen and Eisai, biotech companies for the treatment of Alzheimer's disease (AD), had received marketing approval. Aducanumab (trade name, Aduhelm) is a monoclonal antibody whose main treatment claim is that it clears amyloid- β accumulation from the brain. However, no convincing clinical evidence has been shown thus far that clearing amyloid- β from AD brains results in any benefit to the patient [1].

The reversal by the FDA in contradicting its own decision to not approve aducanumab, took many workers in the field of AD by incredulous surprise, especially because it flew in the face of an expert

AD panel of FDA advisors who had recommended “no approval” when they met the previous November (three of the panel's advisors have since resigned in protest of the FDA reversal). The FDA had agreed at that November meeting to the advisory panel's recommendation of no approval for aducanumab since that is the agency's usual regulatory practice in such matters.

Prior to June 7, the FDA also decided to ignore the recommendation by an Independent Data Monitoring Committee (IDMC) which had also analyzed the clinical evidence submitted for aducanumab and determined the drug did not show any benefit or slow down the rate of AD progression in trial participants given aducanumab. Moreover, aducanumab AD patients, aside from showing no clinical improvement, actually fared worse than patients in one of the placebo arms of the study. The IDMC recommended to the FDA that the phase III trial of aducanumab should be terminated based on their results of a futility analysis which indicated the Biogen trials were unlikely to meet their primary endpoint upon completion. When Biogen and Eisai learned of the IDMC recommendation to terminate the aducanumab trial, they voluntarily scrapped their late-phase III trial,

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worth an estimated 18 billion dollars, a sum representing 4 times the annual FDA budget. Why then did Biogen assume the FDA would be amenable to resume the failed phase III trial and help pave the way for aducanumab approval?

When asked by the media about this, the FDA gave no reasonable explanation for reversing their November 2020 decision or why it trashed its advisory panel. It is mind-numbing seeing that the FDA did not have a prepared statement when that inevitable question was posed by the press. One FDA staffer was quoted by the press to say that the “benefit of aducanumab far outweighed its risk factors.” No follow up to this ludicrous explanation was available which might have inquired how a never-found benefit for aducanumab could affect its risk factors. There was no reasonable explanation given by the FDA to justify the ‘no approval’ reversal since no new clinical evidence had been presented by Biogen between November, when the FDA panel met, and June 7.

The FDA was established in 1906, primarily for the purpose of protecting consumers of unsafe medicines and substances that falsely claimed, without proof, efficacy for some treatment. Approval of a drug by the FDA is considered an extremely difficult and prolonged process that can last 12–15 years at an average cost of \$2.6 billion to the manufacturer before the drug can crawl from the laboratory to the pharmacy shelf. The FDA’s most notable accomplishment came in the 1960s when it rejected thalidomide, a pill designed to help pregnant women sleep better, but it was later revealed to cause significant birth defects.

The decision to approve a drug by the FDA in the US carry so much weight that they are usually adopted by other regulatory drug agencies around the world. The reason is the rigorous, clinical, and statistical analysis given to each drug submitted for commercial application to assure safety and efficacy. In the case of aducanumab, clinical trials by Biogen revealed not only no benefit to AD patients but also cerebral microbleeds and edema which occurred in 30–40% of the patients.

Three key questions need to be urgently addressed:

First, what happened or transpire between November 6, 2020 and June 7, 2021 that made the FDA

reject its expert advisory panel recommendation to “not approve aducanumab” and trash its own decision when it agreed with the advisory committee recommendation?

Second, on what basis did the FDA decide to approve a drug previously considered by an expert panel of FDA advisors and the IDCM to show no benefit to AD patients?

Third, who was able to buy low-cost shares from Biogen stock prior to share prices zooming 38% after June 7, adding \$16 billion to the company’s market value?

The reasons these three questions are important and need an answer seem clear-cut: It is considered medical malpractice to prescribe a drug to patients without informing the patient that the medicine does not work, a practice we call “false hope” [2]. Moreover, it is criminal for a drug manufacturer to willfully allow one of its drugs to enter the consumer market knowing the drug offers no benefit and can cause severe harm to the patients taking the drug.

William Nordhaus, Nobel Prize winner in Economics, has keenly observed that the most egregious form of corporate misconduct is to market a product that will knowingly harm the consumer [3]. Is this where we are headed with Biogen?

DISCLOSURE STATEMENT

Authors’ disclosures available online (<https://www.j-alz.com/manuscript-disclosures/21-0736>).

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