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Aduhelm (aducanumab-avwa) Controversy

Aducanumab (Aduhelm, Biogen) was approved under accelerated approval on June 7, 2021, by the US Food and Drug Administration (FDA) for treatment of Alzheimer's disease. Approval was based on a surrogate marker of reduction of amyloid beta plaques observed in patients treated with aducanumab. In the FDA's approval letter, another confirmatory clinical trial proving clinical efficacy for treatment of Alzheimer's disease was required to gain traditional approval. Much controversy surrounded this initial ground-breaking approval and subsequent marketing rollout.

TROUBLED REGULATORY HISTORY

The Phase III trials, EMERGE and ENGAGE, were identical in study design, with the same primary objective to evaluate the safety and efficacy of aducanumab in early Alzheimer's disease. However, only the high-dose treatment arm in EMERGE was able to demonstrate cognitive improvement. Biomarker substudies conducted throughout both trials showed time- and dose-dependent reductions of amyloid β (Aβ) plaque in small, nonrandom patient populations with subsequent correlation analyses. Approval was based on evidence from EMERGE and ENGAGE, with the FDA claiming the clinical benefit shown with aducanumab is likely due to its ability to change a surrogate endpoint (Aβ plaque). Despite the FDA's advisory committee voting 10-0 to reject approval and its own statistician reviewers rejecting approval, accelerated approval was granted and Biogen was given 8 years to perform postmarketing studies to prove clinical benefit to support its use in the treatment of Alzheimer's disease. Three members of the advisory committee ultimately resigned over this decision.

FINANCIAL IMPLICATIONS

With an initial launch price of $56,000 per year in 2021, aducanumab was forecasted to eventually treat up to 6 million people. Biogen budgeted nearly 3 times the drug's development costs for a marketing campaign to push back at the complaints of the high price. Ultimately, Biogen cut the price to approximatley $28,000 a year later. While Biogen appeared to have cleared regulatory hurdles with its FDA approval, Medicare refused to cover aducanumab for patients who were not enrolled in a clinical trial. Private insurers followed suit, restricting coverage. Medicare cited the lower standard of proof needed for accelerated approval as a reason to refuse coverage.

CONTROVERSY

The approval process and aducanumab's price tag triggered criticism and led Congress and the FDA to conduct investigations into the relationship between Biogen and key figures at the agency. The House Oversight Committee's investigation discovered that FDA and Biogen staff worked unusually closely in order to massage poor study results and changed study endpoints. The nonsignificant benefit found in the trial later was identified as resulting from faster than expected decline in the placebo

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group, rather than slowed decline in the treatment group. FDA statisticians who questioned the data were kept out of meetings. Some of the materials presented by Biogen at the advisory committee meeting were written by FDA staff. The House report also found dozens of contacts between FDA and Biogen that should have been officially recorded but were not. Finally, the House report found that the original list price of the drug was not commensurate with the drug's research and production cost; it appeared to be driven by the company's "ambition to make history."

FUTURE DIRECTIONS AND IMPLICATIONS

As a result of the controversy surrounding aducanumab's approval, including the high price tag without reasonable expectation of significant cognitive benefit, Biogen has decided to abandon the drug's development. Its rights will revert to its original developer, Swiss company Neuroimmune. Biogen is halting the postmarketing confirmatory trials requested by the FDA as condition of approval and plans to reprioritize and focus on its newly approved Alzheimer's disease drug, lecanemab (Leqembi).

The accelerated approval process, launched in 1992, has been under scrutiny for lax oversight by the FDA to force drug companies to complete postmarketing trials by the agreed-upon timeframes. Following the House Oversight Committee report, the Office of Inspector General launched an investigation into the accelerated approval process. One report has been published detailing delays in completing these required postmarketing trials, with an additional report expected in 2024.

With Medicare's refusal to cover aducanumab for patients not enrolled in clinical trials, industry may become more wary of the accelerated approval process, on which several drugs have been approved over the past many years. Industry now may worry that these approvals could result in payers' refusal to cover high-price drugs, despite achieving marketing status.

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