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## Publication Info

Published in *Lancet Regional Health Americas*, Volume 20, 2023, pages 100467-.
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# Impacts of FDA approval and Medicare restriction on antiamyloid therapies for Alzheimer's disease: patient outcomes, healthcare costs, and drug development

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The Lancet Regional Health - Americas 2023;20: 100467
Published Online 1 March 2023
https://doi.org/10.1016/j.lana.2023.100467

## Summary

**In 2021, the US Food and Drug Administration (FDA) granted approval to aducanumab, an antiamyloid antibody for early-stage Alzheimer's disease, despite a lack of clear clinical evidence demonstrating the drug's cognitive benefits. The manufacturer initially priced the drug at a staggering $56,000 per year, a price that was later reduced to $28,200. Unfortunately, these costs do not include the additional expenses associated with monitoring the treatment. However, the Centers for Medicare and Medicaid Services (CMS) recently announced that they will only cover individuals enrolled in clinical trials and will limit coverage of future antiamyloid antibodies. This discrepancy between the FDA and CMS positions has caused confusion and concerns for patients who could potentially benefit from antiamyloid therapy. It is important to acknowledge the clinical and economic uncertainties surrounding aducanumab and its potential impacts on future antiamyloid drug development and approval processes. The FDA's approval, despite limited clinical evidence, raises questions about the integrity and rigor of the approval process. The drug's high cost also raises accessibility concerns, especially for those without insurance or sufficient financial resources. Given the CMS's limited coverage policy, it's critical to evaluate the long-term implications of this decision on future antiamyloid drug development. Without adequate support and coverage from insurance providers, the development and approval of future Alzheimer's treatments may be hindered. In summary, the approval and pricing of aducanumab, coupled with the CMS's limited coverage policy, has created a confusing and concerning landscape for Alzheimer's patients. It's important that stakeholders, including patients, clinicians, insurers, and regulatory bodies, work together to address these challenges and ensure that individuals with Alzheimer's have access to effective, affordable treatments.**

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Keywords: Aducanumab; Alzheimer's disease; Amyloid β plaque

## Introduction

Among treatments being tested to slow the progression of Alzheimer's disease (AD) are amyloid-targeting therapies that reduce the buildup of insoluble amyloid β (Aβ) plaque, a prominent biomarker of the disease.[1–3] Clinical trials have attempted to assess the potential causative relationship of Aβ buildup with progressive cognitive decline.[4] An antiamyloid human monoclonal antibody, aducanumab, was controversially granted fast-track FDA approval in June 2021 after demonstrating a reduction in Aβ; however, its ability to halt cognitive decline in early AD patients is unclear, and adverse events are common.[2,5]

Various cost-effectiveness analyses have revealed that the initial manufacturer-set annual cost of $56,000 is unfavorable, considering the efficacy demonstrated in clinical trials.[6–8] In response to the inconclusive clinical benefits of aducanumab, the US Centers for Medicare and Medicaid Services (CMS) announced the agency would not cover aducanumab treatment except for patients in clinical trials and that it would require additional studies for any future antiamyloid antibodies approved by the FDA.[9,10]

Many new antiamyloid therapies are still in development.[4] Findings from a recent 18-month clinical trial of one such treatment, lecanemab, demonstrated moderately less decline than placebo on measures of cognition and function.[3] We present a discussion of the issues leading up to and resulting from the FDA approval of aducanumab and the CMS stipulations for covering aducanumab and future FDA-approved antiamyloid antibody treatments.

## Clinical evidence and FDA approval of aducanumab

To understand the controversy surrounding the FDA approval of aducanumab, it is crucial to recognize discrepancies that may have contributed to the

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contradictory results of the pivotal phase III trials, EMERGE and ENGAGE. Both trials were identical in study design with the same primary objective to evaluate the safety and efficacy of aducanumab in early AD. However, the implementation of certain study protocols and the premature termination of both trials may have contributed to the discordant results, where the high-dose treatment arm in EMERGE was the only arm among both trials to demonstrate cognitive improvement.[2]

Biomarker sub-studies were conducted throughout both trials, showing time- and dose-dependent reductions of Aβ plaque and tau deposition in small, nonrandom patient populations with subsequent correlation analyses of the clinical endpoints, the Aβ plaque reductions, and the phosphorylated tau (p-tau) reductions. The decrease of Aβ plaque and p-tau had a positive correlation with one another in both EMERGE and ENGAGE; however, modest correlations were observed between the biomarkers and two of the four clinical endpoints in EMERGE.[2]

## Limited generalizability beyond trial participant pools

Biogen was granted fast-track FDA approval for aducanumab in June 2021 based on the evidence from EMERGE and ENGAGE, with the FDA claiming that the clinical benefit shown with aducanumab is likely due to its ability to change a surrogate endpoint (Aβ plaque).[5] Consequently, the generalizability of the EMERGE and ENGAGE results is now of greater importance because it is fundamental to commercial use. However, the baseline demographics of both trials featured racial and ethnic distribution that was uneven: 74–80% of patients were Caucasian, 2–4% of patients were Hispanic or Latino, and 0.2–1% of patients were Black or African American.[2] Given that African Americans and Hispanics are at the highest risk for developing AD, this imbalance constitutes an inaccurate representation.[11] Furthermore, approximately 80% of participants at baseline were in the mild cognitive impairment (MCI) stage of AD, yet the mild stage of AD is typically the point of diagnosis for patients.[2,12] Therefore, it is difficult to measure the efficacy of aducanumab in early AD patients as a whole. With that said, the lack of generalizability within EMERGE and ENGAGE causes concern regarding the actual efficacy of aducanumab for treating early AD.

Following the FDA's controversial approval of aducanumab, Biogen and Eisai conducted a phase III clinical trial of lecanemab, which, like aducanumab, is an Immunoglobulin G1 human monoclonal antibody that targets Aβ. The results of the 18-month trial were published in November 2022 with the promise of improvement over EMERGE and ENGAGE regarding the generalizability of the patient population.[3] Patients received one biweekly dose of lecanemab (10 mg/kg) via intravenous infusion. In this study, CLARITY AD, more patients with mild dementia due to AD were included: ~38% with mild dementia due to AD, ~62% with MCI due to AD.[3] However, representation of the Hispanic and Black patient populations, while greater than in EMERGE and ENGAGE, was still not generalizable AD population in the real world: ~77% Caucasian patients, ~12% Hispanic patients, ~2.5% Black patients.[3,11] The authors noted moderate improvement in cognition among patients treated with lecanemab versus those given a placebo; however, adverse events were associated with treatment. Future trials with longer timespans are required to ascertain the long-term efficacy and safety of lecanemab.

## Healthcare cost and cost-effectiveness

It is important to note that future pricing of antiamyloid therapies could be influenced by the Inflation Reduction Act (IRA) of 2022, which includes provisions aimed at reducing prescription drug costs for Medicare beneficiaries and the US federal government.[13] One provision contained within the IRA requires the federal government to negotiate prices for certain drugs covered under Medicare Part B and Part D with the highest total spending, beginning in 2026.[13] The aim of this provision is to establish a "maximum fair price," which would ultimately decrease out-of-pocket drug costs.[13] Currently, the Department of Health and Human Services (HHS) does not negotiate prices for drugs covered under Medicare Part B; instead, providers are reimbursed based on the Average Sales Price (ASP) plus 6%.[13] Over the next 10 years, $98.5 billion in Medicare savings is anticipated due to the IRA. Drugs excluded from this provision are those less than thirteen years old, including for biologics such as aducanumab, and future antiamyloid antibodies.[13] In the meantime, while aducanumab, and potentially lecanemab, are excluded from the requirement to negotiate costs, HHS will continue its reimbursement based on ASP plus 6%; this will ultimately result in profound Medicare spending as newer antiamyloid drugs become FDA-approved.[13]

When evaluating the overarching cost of living with AD or other dementias, it is essential to consider concomitant medications, provider office visits, Medicare copayments, coinsurances, and services that Medicare or other supporting agencies do not cover.[11] Aducanumab was initially set at an annual price of $56,000 per patient. When applying results from EMERGE and ENGAGE to the AD population, patients would gain an average of 3 months in the MCI stage and one month in mild dementia at a high cost.[6] In a cost-effectiveness analysis conducted by Whittington and colleagues, results indicated minimal health improvement outcomes at an exorbitant cost to the patient.[6] If despite its high price, it was found to lower utilization of

costlier downstream healthcare such as emergency room visits, hospitalization, and nursing home/long-term care placement, its use would have been attractive since it would reduce overall healthcare costs.

Results from willingness-to-pay (WTP) price threshold analyses indicate that a discount upwards of 95% of Biogen's annual launch price (thus, a yearly cost ranging from $2950 to $5960) would be necessary for the treatment to be considered cost effective.[6] In December 2021, Biogen announced the reduction of the annual wholesale acquisition cost (WAC) of aducanumab from $56,000 to $28,200 in hopes of reducing direct costs to the patient.[14]

Ross and colleagues then conducted a cost-effectiveness analysis, assessing the impact of the reduced cost of aducanumab, and the results demonstrated that aducanumab is not likely to be cost-effective if priced above $3000 per year.[7] Currently, at half of its original launch price, aducanumab remains not cost effective.[7] Table 1 summarizes the findings of three cost-effectiveness analyses from the initial launch price of $56,000 per year and the reduced price of $28,200 per year.[6–8] Eisai Co., Ltd. has reportedly set the list price for lecanemab to US $26,500 per year.[15] Thus, its greater effectiveness will translate to a lower incremental cost-effectiveness ratio and more favorable cost-effectiveness determination.[16]

## Adverse effects and additional costs

The most prevalent and debilitating adverse effect of aducanumab, amyloid-related imaging abnormalities (ARIA), also contributes to the aforementioned cost of aducanumab treatment.[17] Characterized by brain swelling and microhemorrhages, ARIA is observed via magnetic resonance imaging (MRI).[18] Of the participants in EMERGE and ENGAGE, 30% experienced events of ARIA, with the highest frequency observed primarily in ApoE ε4 carriers who received a dose of 10 mg/kg$^2$. Current prescribing information recommends a target dose of 10 mg/kg for patients receiving aducanumab therapy, thus exposing patients to a higher risk of developing events of ARIA.[19]

MRIs before initiation and periodically throughout treatment are required for patients receiving aducanumab to mitigate the risk of ARIA.[19] The additional total cost of three brain MRIs for those experiencing ARIA costs the patient an additional $765.[6] In addition to costs associated with ARIA, aducanumab treatment includes fees from intravenous (IV) administration and long-term care; all of which instills an additional financial burden upon patients and caregivers.[6]

Infusion-related reactions and ARIA are the most prominent adverse effects of lecanemab administration as well, as demonstrated by CLARITY AD.[3] In clinical trials, although events of ARIA were observed in numerically fewer participants receiving lecanemab compared to aducanumab, differences in drugs used and in clinical trial design do not allow for a direct comparison of the two agents.[3] Future cost-effectiveness analyses for lecanemab should consider additional costs of infusion-related reactions, ARIA, intravenous administration, and patient monitoring.

| | Health care system perspective | | | Modified societal perspective | | | Source |
|---|---|---|---|---|---|---|---|
| | Aducanumab | Supportive Care | Incremental | Aducanumab | Supportive care | Incremental | |
| **$56,000 initial annual launch price** | | | | | | | |
| Drug costs ($) | 199,000 | 0 | 199,000 | 199,000 | 0 | 199,000 | Whittington et al., 2022[12] |
| Other costs ($) | 347,000 | 342,000 | 5000 | 639,000 | 636,000 | 3000 | Whittington et al., 2022[12] |
| Total costs ($) | 546,000 | 342,000 | 204,000 | 838,000 | 636,000 | 202,000 | Whittington et al., 2022[12] |
| QALYs | 3.467 | 3.313 | 0.154 | 3.097 | 2.938 | 0.159 | Whittington et al., 2022[12] |
| ICER ($/QALY) | – | – | 1,330,000 | – | – | 1,270,000 | Whittington et al., 2022[12] |
| **$28,200 modified annual price** | | | | | | | |
| Drug costs ($) | 119,000 | N/A | 119,000 | 119,000 | N/A | 119,000 | Ross et al., 2022[13] |
| Other costs ($) | 129,100 | 118,000 | 11,100 | 214,100 | 205,200 | 8900 | Ross et al., 2022[13] |
| Total costs ($) | 248,100 | 118,000 | 130,100 | 333,000 | 205,200 | 127,800 | Ross et al., 2022[13] |
| QALYs | 5.081 | 4.948 | 0.133 | 5.081 | 4.948 | 0.133 | Ross et al., 2022[13] |
| ICER ($/QALY) | – | – | 981,000 | – | – | 964,000 | Ross et al., 2022[13] |
| **$56,000 initial annual launch price** | | | | | | | |
| Total costs ($) | 225,440 | 75,550 | 179,890 | – | – | – | Sinha et al., 2022[14] |
| QALYs | 2.93 | 2.46 | 0.47 | – | – | – | Sinha et al., 2022[14] |
| ICER ($/QALY) | – | – | 383,080 | – | – | – | Sinha et al., 2022[14] |

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life years; N/A = not applicable. A summary of the outcomes from three different cost-effectiveness analyses utilizing the initial $56,000 annual launch price of aducanumab and the modified price of $28,200 are shown. The outcomes presented are derived from Markov models created by their respective authors. The Markov model from Whittington and colleagues as well as Ross and colleagues is representative of a life-time time horizon. The Markov model from Sinha and colleagues is representative of a five-year time horizon.[12–14]

***Table 1:*** **Cost-effectiveness studies of aducanumab.**

## Centers for Medicare and Medicaid Services national coverage determination

In April 2022, CMS announced that it would cover FDA-approved antiamyloid antibodies while additional efficacy data are collected in trials approved by CMS, a requirement known as coverage with evidence development (CED).[9] Furthermore, since aducanumab was approved based on biomarker efficacy rather than clinical efficacy, aducanumab will only be covered for individuals enrolled in a CMS-approved randomized controlled study.[10] CMS representatives assured that transparent and trusted clinical evidence evaluating risk versus benefit was utilized to ultimately make an informed decision for its beneficiaries.[9] Within the National Coverage Determination (NCD), CMS alluded to a plethora of reasons for restricting coverage for those seeking aducanumab treatment, including the conflicting results between identical trials, limited generalizability of the trials, significant adverse effects, as well as further discrepancies within the clinical evidence.[9] Of note, none of their reasons included the price of aducanumab.

CMS plans to restrict coverage for future antiamyloid antibodies as well, even if clinical trials show positive results that subsequently lead to traditional FDA approval.[10] The agency proposed that to more accurately reflect the overall Medicare population; future research investigating antiamyloid antibodies should include prospective comparative studies that include patients with AD and multiple medical comorbidities.[10] Gantenerumab, lecanemab, and donanemab fall within the antiamyloid antibody drug class.[10] Phase III results for gantenerumab did not demonstrate clinically meaningful and statistically significant benefit.[20] Additionally, the FDA decided not to grant accelerated approval to Eli Lilly's donanemab.[21] In contrast, phase III results for lecanemab were just recently published, indicating that lecanemab met all primary and secondary efficacy endpoints.[3,10] Both the FDA and CMS require future randomized controlled trials to confirm the ability of antiamyloid antibodies to improve cognition in early AD patients.[5,9] However, there is an undeniable difference in the determination of effectiveness between the FDA and CMS based on their conflicting positions on the use of aducanumab in treating early AD.

## Effect of aducanumab approval on medicare costs

Aducanumab would be billed through Medicare Part B for Medicare enrollees since outpatient hospital visits are required for administration.[22] When examining the impact of the FDA approval of aducanumab on Medicare Part B premium rates, the 2022 premium included a contingency margin to cover projected spending for aducanumab, which posed an increased cost to its beneficiaries.[22] However, CMS's NCD for antiamyloid antibody coverage resulted in lower-than-projected spending in 2022 and subsequently led to reduced premiums for Medicare Part B beneficiaries in 2023.[22] The standard monthly premium for Medicare Part B enrollees for 2023 will be $164.90, with an annual deductible of $226, a decrease from 2022 by $5.20 and $7.00, respectively.[22] The FDA has approved lecanemab via the Accelerated Approval pathway. If CMS decides to cover it, premiums might be impacted due to the reported annual price of $26,500.[23]

Many older adults have dual coverage through Medicare and Medicaid, and it is vital to recognize the implications of aducanumab's approval on Medicaid spending. Although AD affects more than 6 million individuals nationally, it is estimated that 67,000 Medicaid beneficiaries are prescribed medications for AD.[24] If a mere 25% of Medicaid beneficiaries were initiated on aducanumab therapy, Medicaid would face substantial costs of approximately $720 million annually.[24] The states' share would be $230 million, and the federal share would be $490 million.[24] However, with effective treatment, as suggested by one study, there would be substantial budgetary savings to US state Medicaid programs from reduced nursing home use.[25]

## Effect of aducanumab approval on future drug development and approval

The FDA approval of aducanumab was based on the reduction of the surrogate endpoint, Aβ plaque, which may initiate downstream effects of the Aβ cascade hypothesis that may possibly result in cognitive improvement.[26] Because there are insufficient data to support this idea, an additional post-approval trial to confirm the anticipated clinical benefit is now underway. Though not always confirmatory, changes in surrogate endpoints may suggest clinical improvement of disease states through pathophysiological mechanisms.[26] The ambiguity surrounding whether a change in surrogate endpoints translates to clinically relevant outcomes may serve as a framework for re-evaluating any existing therapies approved on a similar basis, especially in the case of donanemab, which is known to a remarkably high Aβ clearance.[27,28] Findings from subsequent research may influence the FDA to set more stringent parameters within the drug approval process. Additionally, stricter coverage standards set by CMS and a higher evidentiary bar set by the FDA may encourage drug manufacturers to construct more rigorous study designs and proper implementation that would ultimately yield more robust results.

## Conclusion

The troubling FDA approval of aducanumab based on conflicting evidence, the decisions by its developers to market it at a cost to patients that is not justified by its marginal clinical benefit when compared with supportive care, and the CMS decision to limit aducanumab coverage to patients enrolled in RCTs leaves early AD

patients with very limited access to the only approved AD treatment. Moreover, the decision by CMS to restrict Medicare coverage of future antiamyloid antibodies places barriers to future treatments of this type even if they demonstrate clinical benefit before FDA approval. Findings from trials of lecanemab suggest the antiamyloid antibodies approach may, in fact, hold the promise of greater clinical benefit, giving hope to patients with AD. It may be appropriate for CMS to reconsider its NCD restriction on all antiamyloid therapies. Consequently, there is an irrefutable need for further research to guide prescribing practices. Providers must serve as patients' resource in the interim by engaging in transparent risk-benefit conversations regarding this therapy.

#### Contributors

RB, JN, BLL, and IY participated in the conception of the viewpoint. RB and JN led the writing of the initial drafts of the manuscript on which all authors commented, and all authors agreed with the decision to submit for publication.

#### Declaration of interests

The authors declare no competing interests. No author received an honorarium for contributing to this paper.

#### Acknowledgments

Funding: This viewpoint received no funding from any agency in the public, commercial, or not-for-profit sectors.

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