Summary

KEY FINDINGS

	aducanumab (Aduhelm™, Biogen)
Evidence Rating	"Insufficient" (I) to show a net health benefit for patients with mild cognitive impairment due to Alzheimer's disease, as well as for patients with mild Alzheimer's disease.
Annual Price	$56,000
Annual Health-Benefit Price Benchmark	$3,000-$8,400
Change from Annual Price Required to Reach Threshold Price	85-95% discount

"The clinical trial history and evidence regarding aducanumab are complex. We have spent eight months analyzing the study results, talking with patient groups and clinical experts, and working with the manufacturer to understand their position. At the conclusion of this effort, despite the tremendous unmet need for new treatments for Alzheimer's disease, we have judged the current evidence to be insufficient to demonstrate that aducanumab slows cognitive decline, while it is clear that it can harm some patients. Nonetheless, the FDA has approved this drug, and if Medicare and private insurers choose to provide coverage, millions of patients and families will face the question of whether to use it -- which means many patients and families will suffer financial toxicity without knowing whether they are taking a drug more likely to help them than hurt them. The company had another path open to them. They could have priced in line with our current best estimate of clinical value at a tenth of their current list price and still expected to make billions of dollars each year. It is unfortunate that they did not choose such a path."

– ICER Chief Medical Officer, David Rind, MD

THEMES AND RECOMMENDATIONS

- To prevent patients and families from being misled, patient groups, the manufacturer, and clinicians should accurately characterize the potential benefits of aducanumab as a slowing of decline of cognition and function and avoid using terms such as "improvement" or "return of quality of life" in all personal statements and advertising.
- Whether aducanumab is widely prescribed or not, health systems, manufacturers, payers, and the FDA should take steps now that will reduce disparities and improve equitable access to dementia diagnosis, management, and future new therapies.
- For AD, the FDA should act quickly to set a clearer regulatory framework in place by specifying a threshold range for amyloid clearance that will be

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accepted going forward as "reasonably likely" to provide patient benefit. More broadly, the FDA should take concrete steps to become clearer about the way it engages its advisory committees and to be transparent and consistent in its designation of surrogate outcomes and the timing of its decisions to use the accelerated approval pathway.

- Clinicians and clinical specialty societies should bear witness to the unmet needs of patients and families with AD to support broad consideration of the value of emerging therapies. But all clinicians and specialty societies should exercise their obligation to provide objective guidance on interpreting the uncertain data on aducanumab, and should advocate for fair pricing and for affordable and equitable access to all available treatments.

Clinical Analyses

KEY CLINICAL BENEFITS STUDIED IN CLINICAL TRIALS

Alzheimer's disease (AD) is a fatal neurodegenerative brain disease characterized by the progressive accumulation of beta-amyloid protein plaques and neurofibrillary tangles; these are hypothesized to damage neurons and lead to the loss of cognition and physical functioning. AD affects almost six million people in the United States (US), with more women than men affected and Black Americans at a higher risk of developing the disease. Symptoms of AD include impairment of memory, language, executive function, and visuospatial function that affects one's ability to function. Other symptoms include changes in mood or personality and sleep disturbances. Eventually, patients may require around-the-clock in-home or institutional care. The average life expectancy of patients with AD is four to eight years. As the disease progresses, caregiver impact—most often done by unpaid family members and friends—increases significantly. Caregivers can suffer significant negative physical, financial, and emotional outcomes from the strain of caregiving.

Current treatment of AD is focused on supportive care, which may include treatment of dementia symptoms with medications that do not alter the course of the disease. Because of the devastating burden of AD, there is a great need for disease-modifying treatments that slow or stop progression of the disease.

Aducanumab ("aducanumab-avwa"; Aduhelm™, Biogen), a human monoclonal antibody that promotes clearance of beta-amyloid plaques from the brain, is a potentially disease-modifying treatment that was granted accelerated approval by the US Food and Drug Administration (FDA) on June 7, 2021 for patients with AD. It is given as an intravenous (IV) infusion every four weeks.

Aducanumab was evaluated in two identical, mostly contemporaneous Phase III randomized clinical trials (RCTs), ENGAGE and EMERGE. The trials randomized patients with early AD (i.e., mild cognitive impairment [MCI] or mild dementia due to AD) to low- or high-dose aducanumab or placebo (exact dosing depended on the presence or absence of a genetic marker of AD risk, apolipoprotein ε4 [APOE ε4]). In both trials and at all doses, aducanumab effectively removed beta-amyloid. The primary clinical outcome was change in mean score on the Clinical Dementia Rating Scale – Sum of Boxes (CDR-SB). Midway through the trials, the trial protocol was amended such that the high-dose group was titrated to 10 mg/kg, regardless of APOE ε4 status (post-Protocol Version 4 [PV4]). In March 2019, ENGAGE and EMERGE were terminated following a prespecified interim analysis for futility. Subsequent analyses revealed a possible positive treatment effect from EMERGE (Table 1), though a important difference

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in CDR-SB has not been clearly defined. However, results from ENGAGE failed to detect any improvement in CDR-SB in the high-dose group compared with placebo. Analyses of secondary endpoints were consistent with the primary endpoint result in each trial (positive in EMERGE, negative in ENGAGE).

The manufacturer explored possible explanations for the discordant results between the two trials; they concluded that the timing of PV4 allowed more patients in EMERGE than ENGAGE to receive the full high-dose regimen (28.8% vs. 22.3%) and that randomization had failed to balance "rapid progressors" in ENGAGE.

Table 1. Change in CDR-SB Compared with Placebo According to Analysis Method

Clinical Trial	Low-Dose Aducanumab*	High-Dose Aducanumab*
ITT Population		
ENGAGE (n=1647)	-0.18 (-0.47, 0.11)	0.03 (-0.26, 0.33)
EMERGE (n=1638)	-0.26 (-0.57, 0.04)	-0.39 (-0.69, -0.09)†
Summary Estimate from Meta-Analysis	*-0.21 (-0.43, 0.00)*	*-0.18 (-0.60, 0.24)*
Post-Hoc Analysis Opportunity-to-Complete Population‡		
ENGAGE (n=956)	-0.12	0.08
EMERGE (n=981)	-0.27	-0.36†
Post-Hoc Analysis Post-PV4 Population		
ENGAGE (n=790)	-0.35 (-0.88, 0.18)	-0.48 (-1.02, 0.06))†
EMERGE (n=887)	-0.42 (-0.94, 0.10)	-0.53 (-1.05, -0.02)†
Summary Estimate from Meta-Analysis	*-0.39 (-0.76, -0.01)†*	*-0.51 (-0.88, -0.13)†*

ITT: intention-to-treat, kg: kilogram, mg: milligram, N/A: not applicable, PV4: Protocol Version 4

*The initial dosage of aducanumab was based on APOE ε4 status. APOE ε4+ patients were titrated to 3 mg/kg in the low-dose group and 6 mg/kg in the high-dose group; APOE ε4- patients were titrated to 6 mg/kg in the low-dose group and 10 mg/kg in the high-dose group (ITT population). After PV4 was implemented, APOE ε4+ patients were titrated to the same dosage as APOE ε4- patients (Post-PV4 group).

†p<0.05.

‡Opportunity-to-complete population: participants in the ITT population who had the opportunity to complete the week 78 visit by March 20, 2019.

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Pooled safety data from the two trials showed that about 35% of patients on aducanumab experienced amyloid-related imaging abnormalities (ARIA), whose clinical effects can range from asymptomatic to severe. Although the majority of patients were asymptomatic or had symptoms such as headache, confusion, or dizziness that resolved with temporary stoppage of the drug, 6.2% of participants receiving the high dose of aducanumab discontinued the drug due to ARIA. Furthermore, some patients experienced bleeding into brain tissue; one death in the Phase Ib trial was attributed to this.

We believe it is possible that ENGAGE and EMERGE found different results because of the explanations put forward by the manufacturer related to rapid progressors and exposure to full-dose therapy; however, other explanations are equally or more likely. The post-hoc analyses do not consistently explain what was seen in the low- and high-dose arms of the trials, and one alternative explanation is that the differences between the trials are due to chance. Furthermore, there is disagreement about whether the degree of improvement seen in EMERGE is clinically important, and the relationship between clearance of beta-amyloid in the brain and clinical improvement has yet to be conclusively demonstrated, with negative results from more than 20 other trials of anti-amyloid drugs. Additionally, aducanumab can cause symptomatic ARIA. Given the certainty that harms can occur in patients treated with aducanumab and uncertainty about benefits, we rate the evidence to be insufficient to determine the net health benefit of aducanumab ("I") in patients with MCI and mild AD. Although clinical trials for aducanumab did not include patients with moderate or severe AD, prior clinical trials of anti-amyloid drugs have suggested a lack of benefit in this population, and thus the potential that aducanumab would benefit patients with severe forms of AD is even less likely.

Economic Analyses

Table 2. Base-Case Annual Cost-Effectiveness Threshold Pricing for Aducanumab

Health Care System Perspective	Annual Price*	Annual Price at $100,000 Threshold	Annual Price at $150,000 Threshold
QALYs Gained	$56,000	$2,950	$5,110
evLYG	$56,000	$4,260	$7,090
Modified Societal Perspective	**Annual Price***	**Annual Price at $100,000 Threshold**	**Annual Price at $150,000 Threshold**
QALYs Gained	$56,000	$3,740	$5,960
evLYG	$56,000	$5,330	$8,360

evLYG: equal value of life years gained, QALY: quality-adjusted life year

*The prices presented in this table are not inclusive of the 6% mark-up. The model adds a 6% mark-up to these annual prices.

Economic Analyses

LONG-TERM COST EFFECTIVENESS

We estimated the cost effectiveness of aducanumab in addition to supportive care as compared to supportive care alone, assuming blended efficacy from ENGAGE and EMERGE. Base-case results were calculated from both the health care system perspective and the modified societal perspective. The base-case cost-effectiveness threshold prices for aducanumab ranged from an annual price of $2,950 to $8,360 (Table 2 above).

In summary, we judge that the evidence is insufficient to conclude that the clinical benefits of aducanumab outweigh its harms or, indeed, that it reduces progression of AD in patients with MCI and mild AD. If blended efficacy results are used from the Phase III trials, our base-case analyses suggest that proposed pricing for aducanumab as has been stated by the manufacturer would not be in alignment with its clinical benefits. If aducanumab were determined to have no net health benefit, no threshold price could be generated to guide considerations of fair pricing.

VOTING RESULTS

- CTAF voted unanimously that the evidence is not adequate to demonstrate that aducanumab is superior to supportive care. CTAF cited the discordant results from ENGAGE and EMERGE as well as the fact that the degree of improvement seen in EMERGE is of uncertain clinical significance. Further, it was noted that the relationship between beta-amyloid clearance and clinical benefit has yet to be demonstrated.

- A majority of CTAF voted that the acuity of need for an AD treatment represents a very high priority. Currently, there is only one potentially disease-modifying therapy for AD. Prior to the approval of aducanumab, between 2002 and 2021, no new drugs were approved for the treatment of AD.

- CTAF also voted that based on the magnitude of the lifetime impact of AD, very high priority should be given to an effective treatment. As noted, delaying or halting progression of AD would substantially improve the quality and, possibly, the length of life of patients.

- CTAF was split on whether aducanumab would have a negative effect or make no difference on a patient's ability to achieve life goals. In both cases, the votes were driven by the unanimous determination that the evidence is inadequate to demonstrate that aducanumab is superior to supportive care. Based on similar reasoning, CTAF voted that aducanumab would either have a potential negative effect or make no difference in caregivers' ability to achieve major life goals.

- Lastly, a majority of CTAF voted that aducanumab may have a major negative effect on reducing health inequities. Importantly, Black and Hispanic populations have a higher prevalence of disease yet out of 3,268 total participants in ENGAGE and EMERGE, just 19 were Black or African American and only 104 were Hispanic or Latino. In addition, aducanumab is given as an IV infusion every four weeks and it is likely that payers will require either a neurologist or geriatrician to prescribe the drug. These two factors may impact individuals who live in rural areas where academic medical centers are sparser and access to specialists is limited. Relatedly, it may be difficult for patients and their caregivers to travel to infusion centers and take time off from work and/or school. Lastly, the price of aducanumab and the various associated out-of-pocket costs (i.e., travel, amyloid PET, etc.) may have a substantial impact on access to treatment, potentially disadvantaging patients and families in lower socioeconomic classes.

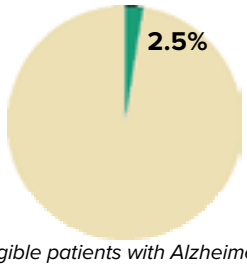
Economic Analyses

POTENTIAL BUDGET IMPACT

In the health care system perspective, approximately 2.5%, or 35,000 out of 1.4 million AD patients eligible for treatment with aducanumab could be treated within five years before crossing the ICER potential budget impact threshold of $819 million per year. When taking a modified societal perspective, approximately 2.6% of the 1.4 million patients eligible for the treatment with aducanumab could be treated, which equates to roughly 36,000 individuals.

Testimony from clinical experts at the public meeting suggested a wide range of clinical uptake of aducanumab, with the majority suggesting numbers well above 100,000 patients over five years. According to our analyses and given that efforts to reach this clinical target would create a short-term potential budget impact that exceeds ICER's threshold, ICER is issuing an access and affordability alert for aducanumab.

The purpose of an ICER access and affordability alert is to signal to stakeholders and policy makers that the amount of added health care costs associated with a new service may be difficult for the health system to absorb over the short term without displacing other needed services, creating pressure on payers to sharply restrict access, or causing rapid growth in health care insurance costs that would threaten sustainable access to high-value care for all patients.



Percent of eligible patients with Alzheimer's disease that could be treated in a given year before crossing the ICER

aducanumab

About ICER

The Institute for Clinical and Economic Review (ICER) is an independent nonprofit research institute that produces reports analyzing the evidence on the effectiveness and value of drugs and other medical services. ICER's reports include evidence-based calculations of prices for new drugs that accurately reflect the degree of improvement expected in long-term patient outcomes, while also highlighting price levels that might contribute to unaffordable short-term cost growth for the overall health care system.

ICER's reports incorporate extensive input from all stakeholders and are the subject of public hearings through three core programs: the California Technology Assessment Forum (CTAF), the Midwest Comparative Effectiveness Public Advisory Council (Midwest CEPAC) and the New England Comparative Effectiveness Public Advisory Council (New England CEPAC). These independent panels review ICER's reports at public meetings to deliberate on the evidence and develop recommendations for how patients, clinicians, insurers, and policymakers can improve the quality and value of health care.

For more information about ICER, please visit ICER's website (www.icer.org).