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Aduhelm, FDA & CMS

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Key Takeaways:

- Aduhelm's Phase 3 clinical trial data offered conflicting evidence of whether the drug improves clinical outcomes in Alzheimer's Disease
- The FDA approved Aduhelm despite a 10-0 recommendation against approval by an independent FDA Advisory Committee
- FDA approval was predicated on Aduhelm's ability to reduce plaque buildup in the brain, *not* on demonstrated clinical effectiveness
- Immediately after FDA approval, Biogen set Aduhelm's list price at $56,000 annually, raising concerns about cost and accessibility
- In January 2022, CMS released a proposed coverage determination for monoclonal antibodies in Alzheimer's treatment, under which Aduhelm is covered only for patients in CMS-approved Randomized Control Trials
- CMS's proposal to eschew offering full coverage for Aduhelm marks a break from historic precedent, under which CMS would consider FDA approval to represent sufficient evidence of clinical efficacy
- The Public Comment period following CMS's proposed coverage decision attracted a record number of comments
- Proponents of CMS's proposal include payers, pharmacy benefit managers, and many academic researchers and neurologists
- Opponents of CMS's proposal include patient advocacy groups and pharmaceutical companies
- The controversy over Aduhelm's approval process raises important questions about the future of the FDA approval process, the relationship between the FDA and CMS, and the future of CMS's "Coverage for Evidence Development" policy

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Introduction/Background

Aducanumab ("Aduhelm") is a monoclonal antibody developed by Biogen that proposes to treat Alzheimer's Disease (AD).[1] Monoclonal antibodies are a class of proteins built to attack or neutralize specific targets in the body. Their effectiveness has been demonstrated in treating numerous diseases, from cancer to COVID-19.[2] Aduhelm is targeted against the amyloid plaques that build up in the brain during AD; the theory is that, in reducing plaque buildup, Aduhelm will reduce the symptoms and progression of AD. Over the past 30 years, more than twenty-five drugs targeting amyloid plaques have undergone clinical trials, and all failed to provide measurable benefits.[3]

How Effective is Aduhelm in treating AD?

Aduhelm completed a Phase 3 Randomized Clinical Trial (RCT) in August 2019, and Biogen announced in October 2019 that it would seek Food and Drug Administration (FDA) approval for Aduhelm, claiming that the drug reduced clinical decline in patients with early AD.[4] This was considered a surprising development, given that the company elected in March 2019 to stop Aduhelm studies, as preliminary data reviews suggested that the drug was unlikely to fulfill its trial

About Alzheimer's Disease

Alzheimer's Disease (AD) is a terrible illness. AD is a disease of the brain that gradually, progressively, and inexorably destroys memory, thinking skills, and ability to undertake simple activities of daily living. Approximately 6 million Americans are currently living with AD, and it ranks as the sixth leading cause of death in the United States, as well as the single leading cause of dementia among older adults.

AD imposes incredible burdens and suffering upon its victims, and upon caretakers and families of victims. It induces the buildup of abnormal proteins in the brain that form "amyloid plaques" and "tau tangles", which interfere with the functioning of neurons, the cells that make up our brain. Gradually, the neurons die, giving brains afflicted with AD a characteristic withered and shrunken appearance.

To date, there is no cure for AD. The only medication with any proven effectiveness in treating AD is a medicine called Donepezil, which may temporarily improve or maintain cognitive function in patients with early-stage, mild to moderate AD. However, Donepezil has only moderate-quality evidence of effectiveness, and an AD cure or effective treatment represents a "holy grail" of pharmaceuticals.

endpoint. Further, an independent monitoring board found multiple safety issues associated with the drug.[5] Biogen's decision to seek approval was predicated upon additional data analysis that purported to show clinical benefit in patients that received a high dose of the medication.[4]

Aduhelm was evaluated in two identical clinical trials, EMERGE and ENGAGE, that were submitted to the FDA as part of its 2020 Biologics License Application.[6] In EMERGE, the cohort receiving high-dose Aduhelm experienced a 23% decrease in their rate of clinical decline compared with patients receiving placebo. However, in the ENGAGE trial, patients on high-dose Aduhelm saw just a 2% decrease in rate of decline compared with placebo - a result that failed to meet the threshold for statistical significance.[7]

Numerous side effects were described in the clinical trials. Among them were brain swelling and brain bleeding - complications that can be fatal. At least one patient's death in an Aduhelm clinical trial was likely caused by brain swelling from the medication. Moreover, approximately 41% of patients in the trial were found to have amyloid related imaging abnormalities (ARIA), brain pathology associated with amyloid plaque that can be visualized on an MRI scan. 64 of the 1,029 patients who participated in an Aduhelm trial were forced to stop the medication due to swelling or bleeding.[8]

FDA Advisory Committee Consideration

In November 2020, the FDA's Peripheral and Central Nervous System (CNS) Advisory Committee met to consider Biogen's application for Aduhelm approval. FDA Advisory Committees are comprised of independent experts who provide advice and recommendation to the agency on technical and scientific issues.[9] These committees generally contain scientific experts, but also often include industry representatives and patient advocates. Though the FDA is not legally bound to adhere to the recommendations of its advisory committees, it does so about 80% of the time, and the FDA overruling one of its Advisory Committees typically occurs in the setting of contentious Advisory Committee

votes.[10] The Peripheral and CNS Advisory Committee voted 10-0, with one abstention, that Aduhelm's trial data did not constitute evidence of effectiveness for the treatment of AD.[11]

The Advisory Committee's judgment drew attention for the argumentative meeting that preceded its decision. At Advisory Committee meetings, representatives from the FDA present on the topic up for consideration; at the November 2020 meeting to consider Aduhelm, the FDA's presentation called Biogen's application "compelling" and "extremely persuasive," descriptors that one committee member criticized as wholly "incongruous" with the trial data.

FDA Approval

In June 2021, the FDA approved Aduhelm through its Accelerated Approval Program, where the agency is permitted to approve, based on a "surrogate endpoint," products that treat "serious or life-threatening disease."[12] As a stipulation of approval, the FDA may require drugs or devices in the Accelerated Approval Program to undergo further testing to demonstrate drug efficacy. In the case of Aduhelm, the FDA considered reduction of amyloid plaque a surrogate endpoint, writing that it is "expected" to predict clinical benefit.[13] This came despite Dr. Billy Dunn, head of the FDA's neurosciences commission, telling the Peripheral and CNS Advisory Board in November 2020 that "We're not using the amyloid as a surrogate for efficacy."[14]

The agency did not limit approval of Aduhelm to patients with mild disease (such as those enrolled in the Aduhelm trials), but instead, for all patients with AD, under the rationale that all AD patients could benefit clinically from plaque reduction.[13,15] Further, the FDA is requiring Biogen to complete a nine-year Randomized Control Trial to evaluate the efficacy of Aduhelm treatment in providing clinical benefit compared with a placebo.[16] Typically, Medicare pays for drugs approved under the Accelerated Approval Process.[17]

Proponents of the FDA's decision note that the approval paves the way for broad access to Aduhelm for the millions of Americans suffering with AD. They also note that the agency's

ruling permits access while allowing for further testing; the agency can remove Aduhelm from the market if clinical trials fail to show benefit. Critics of the decision accuse the FDA of overruling the consensus of its Advisory Board and of ignoring data that demonstrate ambiguous results around Aduhelm's efficacy. They also worry that the FDA has overlooked Aduhelm's serious side effects. Finally, they argue that the approval of Aduhelm based on plaque reduction as a secondary marker may pave the way for the approval of other AD drugs that reduce plaque while showing marginal to no clinical benefit.[3]

The agency's decision provoked considerable backlash amongst the Peripheral and CNS Advisory Committee that had voted against approval. Three members of the committee quit in the days following Aduhelm's approval; Aaron Kesselheim, director of the Brigham & Women's Hospital's Program on Regulation, Therapeutics, and Law, called the decision "probably the worst drug approval decision in recent US history."[18] Kesselheim told STAT News that the Aduhelm decision represents a dangerous precedent because it gives credence to "the idea that a company can turn around and at the last minute seek [accelerated approval] when their primary clinical endpoints in their trials don't reach the level needed for FDA approval."[19]

Cost Considerations

Immediately after Aduhelm's approval in June 2021, commentators noted that Biogen "may be sitting on the most lucrative product in pharmaceutical history."[20] In the hours that followed the FDA's approval, Biogen set the list price for the drug at $56,000 annually. With six million AD patients in the United States, Rachel Sachs notes in *Health Affairs* that "treating just one-third of Americans with Alzheimer's could mean annual drug revenues for Biogen for Aduhelm alone of $112 billion."[3] Aduhelm's coverage will come under Medicare Part B, which covers prescription drugs administered in outpatient settings. In 2019, total Medicare Part B spending was $37 billion.[21] Even if just a fraction of the eligible Medicare beneficiaries with AD opt for Aduhelm treatment, the total cost to American taxpayers could total in the tens of billions annually, dwarfing the spending on other infusion drugs.[22]

One analyst noted that if just 1/6 of American AD patients used Aduhelm at the $56,000 price point, total Medicare Part B spending would double. While CMS is supposedly blind to cost on coverage determinations, it is difficult to ignore that a determination to grant full Aduhelm coverage could increase Medicare expenses by tens of billions of dollars.[22]

Anticipating CMS's National Coverage Determination

Due to the popular interest in Aduhelm and the implications for medication access and national healthcare expenditures, the decision by the Centers for Medicare & Medicaid Services (CMS) on whether to cover Aduhelm was eagerly awaited. A CMS decision, through the Medicare National Coverage Determination (NCD) process, was also expected to shed light on the differing roles that the FDA and CMS play in the process of drug approval and payment. As Dickson et al noted in *Health Affairs*, in contrast to FDA approval, "Medicare NCD decisions are not an all or nothing proposition," as CMS can choose to restrict coverage to specific groups or can delay full coverage as additional evidence about the drug's efficacy emerges.[24] The process by which CMS can choose to limit coverage as additional evidence is collected is known as "Coverage for Evidence Development" (CED), which restricts payment to those participating in CMS-approved studies. It is an option for the coverage of promising drugs and devices that would not ordinarily meet CMS's evidentiary standards, and it is designed to balance issues of access with further evidence gathering.[25]

Finally, CMS's NCD was watched closely by commercial insurers, who often closely follow Medicare's lead on coverage determinations.[26] Nevertheless, even prior to release of the NCD, at least eight Blue Cross Blue Shield affiliates determined they would not cover Aduhelm, while Humana stated it would cover Aduhelm for members similar to the patients participating in the clinical trials.[27]

CMS's National Coverage Determination

On January 11th 2022, CMS released its proposed NCD memorandum covering all FDA-approved monoclonal antibodies targeting amyloid in AD treatment – of which Aduhelm is the only existing option.[28] The NCD proposed covering Aduhelm under a CED process, in which only patients participating in CMS-approved RCTs may obtain coverage. Citing Aduhelm's side effects, including the ~40% of patients in Aduhelm trials who experienced ARIA, CMS noted that it had "significant concerns" about the potential harms imposed on patients treated outside the rigorous guidelines of a clinical trial.[29] CMS's decision to restrict Aduhelm effectively decoupled the FDA's approval decision from CMS's coverage decision; as Rachel Sachs noted in *Health Affairs*, "the FDA's approval decision is usually held out as a proxy for CMS's determination."[3]

The NCD gave a bleak assessment of the evidence supporting Aduhelm's potential clinical benefits. It concluded that there is "insufficient evidence to conclude that the use of monoclonal antibodies directed against amyloid is reasonable and necessary for the treatment of AD."[29] It went on to state that there does not exist sufficient evidence to conclude that any biomarker (e.g. amyloid plaque) has achieved "surrogate status" that predicts clinical benefit in AD. Importantly, while Aduhelm is indeed the only monoclonal antibody currently FDA-approved for AD treatment, there are numerous monoclonal antibodies in development from Eli Lily, Roche/Genentech, and others.[30] These drugs would likely fall under this CMS NCD, given that it applies to all monoclonal antibodies for AD treatment.

CMS outlined numerous requirements for clinical trials under which Medicare would foot the bill for Aduhelm. For one, the clinical trials are required to be RCTs, considered the gold standard for evidentiary development. Additionally, clinical trials are required to occur at a hospital outpatient setting, patients participating are required to have demonstrated AD on a Positron Emission Tomography (PET) scan, and the trials are required to meet specific

diversity benchmarks of tested populations.[29] Notably, just 19 out of 3,285 patients in the major Aduhelm trials were black.[31]

Public Comment on CMS's Aduhelm Determination

A record 9,956 replies were submitted to CMS during its public comment period for the Aduhelm NCD. This period allows stakeholders to publish comments that assess CMS proposals prior to release of the final NCD. This unprecedented swath of public comments can likely be attributed to the enormous interest in drugs effective in AD treatment, as well as the controversy surrounding both Aduhelm's FDA approval and its proposed cost. It should also be noted that many of the 9,956 replies used identical language and may have been part of organized letter-writing campaigns in support or protest of the NCD.[32]

In general, commentors who supported CMS's NCD were aligned with neurologists, state Medicaid agencies, commercial insurers, and pharmacy benefit managers (PBMs). Neurologists submitting comments tended to agree with the independent conclusions reached by the FDA's Peripheral and CNS Advisory Committee around Aduhelm's questionable efficacy, while stakeholders involved in pharmaceutical payments (e.g. payers and PBMs) balked at the gigantic potential costs associated with full Aduhelm coverage.[31, 32] State Medicaid agencies also asked CMS to allow them to limit coverage of Aduhelm, and create prior authorization criteria that would make access to the drug more difficult for their beneficiaries.[33]

On the other hand, a coalition of patient advocacy groups and right-leaning commentators and stakeholders decried CMS's proposed NCD for limiting access. The Wall Street Journal editorial board released an editorial titled, "The Alzheimer's Death Panel," which argued that CMS's proposed limitations on coverage to those participating in RCTs amounted to a bureaucratic death sentence for AD patients.[34] 78 Republican members of Congress signed a letter to CMS demanding broader coverage, accusing the agency of "anti-ageism."[32] Finally, organizations representing patients with Down Syndrome received significant

media attention. Patients afflicted with Down Syndrome are at significantly increased risk of developing early-onset AD, but Down Syndrome patients were excluded from Biogen's clinical trials. Further, CMS's proposed NCD bars patients with neurologic conditions other than AD from trial participation. Thus, many commentors called for a specific Aduhelm trial in patients with Down Syndrome to expand access to this vulnerable group.[35]

Finally, there existed a significant number of commentors who agreed in principle with CMS's decision to limit coverage as more evidence is gathered, but who disputed CMS's stipulations that a) the NCD apply to all monoclonal antibodies targeting plaque in AD, and b) the CMS-approved clinical trials for Aduhelm meet certain stringent requirements.[31, 32] Some commentators also lamented CMS's vagueness around what would constitute "clinically meaningful" benefit in AD patients in future trials.[30]

Where does Aduhelm stand now?

Aduhelm's fate remains in flux. Though the drug has received broad FDA approval, its use may be restricted by CMS to clinical trials, and many commercial payers have outright declined to cover the drug. Many hospitals and health systems around the country, including the Cleveland Clinic and Mass General Brigham, have declared that they will not administer the drug. Already, Biogen has slashed the list price from $56,000 per year to $28,200 per year.[36]

The 30-day Public Comment period for CMS's proposed NCD for Aduhelm closed on February 10th, 2022. A full decision is expected on April 11th. One can assume that the debates over Aduhelm have only just begun. As America awaits CMS's final decision, it is worth exploring some of the important questions raised by CMS's draft NCD.

Questions Raised by the CMS's Proposed Coverage Decision

Should the proposed CED apply to all anti-amyloid monoclonal antibodies for AD treatment?

CEDs often apply to drug classes writ large, and this proposal is no exception. However, given that Aduhelm is the lone monoclonal antibody for the treatment of AD to receive FDA approval, and as other monoclonal antibodies for AD remain in development and trials, independent observers have questioned whether it is fair to subject all approved monoclonal antibodies to the same CED.[30] Future monoclonal antibodies might show significant clinical benefit, far beyond the benefit demonstrated by Aduhelm; in this hypothetical case, as David Holtzman of Washington University in St. Louis has noted, such a drug should "enjoy full Medicare coverage."[32] Moreover, it is also unclear whether stronger emerging evidence from a future monoclonal antibody for AD treatment would affect Medicare coverage for the entire class of drugs. 83% of neurologists surveyed by the Global Alzheimer's Platform Foundation agreed that the results from one drug should not determine whether the entire class needs a CED.[37]

To what extent should CMS impose stringent requirements on clinical trials for drugs approved under the CED process?

CMS has stipulated that coverage for Aduhelm is dependent on patient participation in RCTs. However, several commentators have suggested that CMS should relax its RCT requirement and should cover Aduhelm for patients participating in registry-based studies, given that registry-based studies may draw from a larger, more diverse population. As Mark McClellan and others have written, "large longitudinal post-market studies would likely be more informative than RCTs about some of the important safety questions related to the use of monoclonal antibodies."[30] Moreover, conducting an RCT may not be feasible in all areas of the country. A group of Colorado neurologists wrote in the public comment

period that there is just one site in the state capable of running an RCT, raising accessibility concerns.[32]

To what extent are diversity requirements in clinical trials reasonable?

CMS has proposed diversity requirements for the future clinical trials to ensure that the drug is adequately tested in various sub-populations of patients. These requirements are at least in part because Black and Hispanic patients are more likely to get AD, but less likely to join clinical trials in general.[38, 39] However, CMS did not state what level of statistical confidence is needed in evaluating diverse subpopulations, raising questions about whether the final approval decision might differ across racial or ethnic groups. Would CMS limit coverage to specific racial or ethnic groups if studies show differences in efficacy?

An additional question is whether the diversity requirements imposed by CMS on under the Aduhelm CED would be required for other monoclonal antibody treatments for AD currently in development prior to consideration of full approval. A group from Duke's Margolis Center for Health Policy notes that no current FDA-approved anti-amyloid monoclonal antibody trial meets CMS's proposed diversity standards.[30] Should these trials demonstrate clinical efficacy in AD treatment, would they too be required to conduct additional trials in diverse subpopulations prior to obtaining full coverage?

How does CMS determine what constitutes adequate evidence of efficacy?

Although CMS was clear that the current evidence supporting Aduhelm's clinical benefits was insufficient to obtain full coverage approval, they did not define what evidence might be sufficient. The CED process typically does not set an end date, or define clear success criteria, leaving open the question: what constitutes adequate evidence of efficacy? And what level of cognitive benefit would be considered clinically meaningful? This latter question is particularly controversial, as academic researchers, pharmaceutical companies, payers, clinicians, and patients all likely have differing, subjective opinions of what

constitutes meaningful benefit. Andrew Stern of Harvard Medical School argued that cost-effectiveness is a better barometer of clinical meaningfulness given the likely disagreements across stakeholder groups.[32]

The question of determining a standard of clinical meaningfulness has important implications for ongoing and future trials. Because CMS did not define what evidence would be considered sufficient for approval of monoclonal antibodies for AD, it is unclear whether ongoing studies would be deemed sufficient by CMS even if they meet their FDA-approved trial endpoints. It has been argued that ongoing trials should be permitted to be modified should CMS determine that their endpoints are not sufficient. As of yet, CMS has not adequately defined such endpoints, leaving the value of these ongoing clinical trials up in the air.[30-32]

Conclusion

Aduhelm's complicated path through the FDA and CMS approval processes has raised important questions about the role of each agency in promoting and regulating drug development and access. How these agencies choose to move forward will have profound implications on health systems, insurers, physicians, and – above all – patients.

Discussion Questions:

- What is the proper role of an Advisory Board in the FDA approval process?
- Should cost ever matter in the FDA approval process?
- Does CMS have an obligation to cover FDA-approved drugs and devices?
- To what extent is CMS justified in using payment decisions to keep FDA-approved drugs off the market?
- Could the FDA and CMS coordinate decisions in future cases?
- Should CEDs apply to individual drugs, or drug classes writ large?
- What diversity requirements should new drugs and devices be required to meet?

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