Medicare Coverage of Monoclonal Antibody Treatments for Alzheimer's Disease:
Key Issues from the CMS Proposed Coverage Decision

Authors: Nitzan Arad, Beena Bhuiyan Khan, Elizabeth Staton, Hannah Graunke, Marianne Hamilton Lopez, Mark McClellan

Overview

This Duke-Margolis issue brief summarizes the National Coverage Analysis (NCA) proposed decision memo issued by the Centers for Medicare & Medicaid Services (CMS) for the use of monoclonal antibodies (mAbs) to treat Alzheimer's disease (AD). Our analysis focuses on key questions that would be valuable for CMS to clarify and that should be the subject of comments during the comment period that closes on February 10, 2022. Table 1 summarizes these questions.

Table 1: Key Questions Raised by and Arising from the CMS Proposed Decision Memo

Key Questions
• *Raised by CMS:* Does use of monoclonal antibodies directed against amyloid for the treatment of AD result in a statistically significant and clinically meaningful difference in decline in cognition and function?
• *Raised by CMS:* What are the adverse events associated with the use of monoclonal antibodies directed against amyloid for the treatment of AD?
• Can CMS clarify what evidence is needed for broader coverage of a particular mAb?
• Could positive results from trials already underway, including FDA-approved pivotal RCTs and other NIH-funded studies, support a less restrictive CED requirement (if not broad coverage)?
• Would stronger emerging evidence from a single mAb affect coverage for the class?
• What level of evidence is required for the use of plaque reduction as a surrogate marker to meet the CMS "reasonable and necessary" standard for broader coverage?
• Can CMS, FDA, and other relevant public health agencies implement a coordinated, ongoing process for timely assessment of the status of evolving evidence on mAb products and its implications for Medicare coverage in this important area of unmet medical need?

Aduhelm (aducanumab) received Food and Drug Administration (FDA) approval through its accelerated approval pathway[1] based on the drug's effect on amyloid-plaque removal, a surrogate endpoint, that the FDA concluded was reasonably likely to predict a clinical benefit. As part of the accelerated approval, FDA has required a post-approval randomized controlled trial (RCT) to verify that aducanumab provides the expected clinical benefit on cognition and function. Multiple mAb treatments for AD are being evaluated in ongoing FDA-approved Phase 3 RCTs, with findings on primary outcome endpoints expected over the next several months to years, with the potential for additional accelerated approvals in 2022 and beyond.

CMS coverage is based on an assessment of whether an item or a service is "reasonable and necessary" for Medicare beneficiaries. CMS has defined an item or service as "reasonable and necessary" if it is (1) safe and effective, (2) not experimental or investigational, and (3) appropriate for use in Medicare beneficiaries.[2]

On January 11, 2022, CMS announced its proposed decision to cover the class of anti-amyloid mAbs for the treatment of AD under a **coverage with evidence development (CED) framework**. Per the proposal, anti-amyloid mAbs **will only be covered in CMS-approved RCTs** and trials supported by the National Institutes of Health (NIH) with specific patient enrollment criteria and defined research questions.[3] A final decision is expected this spring, following public comments and CMS's consideration of the comments.

The CMS evidence review informing its proposed decision incorporated over 250 peer-reviewed articles, including information on Phase 3 clinical trials of AD mAbs as well as reports from other agencies, such as the FDA.[4] The CMS analysis centered on the question of whether there is sufficient evidence to conclude that mAb treatment for AD improves the health outcomes of Medicare beneficiaries.

In its proposed decision, CMS determined that the current evidence is inconclusive regarding the effectiveness of mAb therapies to treat amyloid in AD and raises concerns about safety risks caused by mAbs in the absence of proven clinical effectiveness. Consequently, CMS found that there is currently "*insufficient evidence to conclude that the use of monoclonal antibodies directed against amyloid is reasonable and necessary for the treatment of Alzheimer's disease*.**"**

Further, CMS concluded that *"there is some preliminary research that shows promise, but it's far from conclusive and more rigorous individual trials (e.g. RCTs) continue to be needed to determine the clinical benefit of anti-amyloid mAbs for the treatment of AD."* Based on this conclusion, CMS proposed to cover the new class of therapies under CED in the context of an RCT to develop more evidence.

In this analysis, we first summarize the rationale in the proposed CMS coverage criteria and trial requirements. Next, we highlight key areas where comments, revisions, or clarifications could help address the priorities of patient access, equity, and the need for further evidence development. These areas span both findings on the key questions framed by CMS for current coverage, and the implications of the proposed decision for how further evidence will be developed and used for coverage of the class of AD mAb therapies.

Key Findings in the CMS Proposed Decision

CMS's Evidence Review

CMS's evidence review focused on whether clinical trials reported to date provide *"evidence sufficient to conclude that the use of [mAbs] directed against amyloid for the treatment of [AD] improves the health outcomes for Medicare beneficiaries."* We expect that many public comments on the CMS findings will focus on CMS's approach and conclusions from this evidence review, and the proposed decision based on the review. We highlight some of these important considerations here.

Effectiveness of mAbs for the Treatment of AD Patients

CMS conducted a comprehensive review of the relevant peer-reviewed literature relating to aducanumab and other mAb treatments as well as public FDA reports on ongoing mAbs in development. CMS focused on the quality and strength of the evidence supporting the premise that mAbs for AD improve health outcomes, which it defined as a clinically meaningful difference in decline in cognition and function of Medicare patients. CMS highlighted the findings of the FDA's Peripheral and Central Nervous System Drugs Advisory Committee that voted against the approval of aducanumab, stipulating that there was not enough evidence to show that the drug could slow cognitive decline based on its two Phase 3 studies, EMERGE and ENGAGE. CMS also noted that previous anti-amyloid mAbs have failed clinical trials and did not enter the market. Further, with regard to the use of plaque reduction as a surrogate biomarker, CMS agreed with a publication[5] reviewing Phase 3 trial data that *"no biomarker has achieved surrogate status in AD drug development with definite evidence that a change in the biomarker predicts a clinical benefit."* CMS also pointed to a recent meta-analysis[6] of Phase 3 trials for several mAbs, which found *"evidence of statistical significance, but not necessarily clinically meaningful differences in health outcomes."*

While the evidence review was extensive, the Phase 3 trials that CMS referenced primarily involve aducanumab and older mAb treatments that are generally considered less efficacious in removing AD-related plaques. They did not include new candidates in the class that are in pivotal Phase 3 trials. Newer mAbs, such as lecanemab and donanemab, have been the subject of only limited published studies to date.

Safety of mAbs for the Treatment of AD Patients

CMS then reviewed and summarized the safety issues associated with AD mAbs, stating that "*antiamyloid mAb trials have demonstrated harms such as headaches, dizziness, falls, and amyloid-related imaging abnormalities (ARIA). At the time of this writing, there is ongoing assessment of whether the use of an antiamyloid mAb has caused or contributed to death.*" It also pointed to a study that indicates that "*ARIA was found in approximately 40% of participants in the phase 3 studies of aducanumab, and approximately one-quarter of these patients experienced symptoms.*"

CMS concluded that due to a lack of clear clinical benefit and the frequency of significant adverse events, the evidence does not support that the benefits outweigh the harms of mAb treatments for Medicare beneficiaries. The discussion of safety issues highlighted that the proposed population for coverage was very broad, including many subgroups of patients with conditions that could exacerbate risks from treatment side effects and many that may not respond to treatment (in contrast to other accelerated approvals for treatment for an unmet need that were designed for more targeted populations and involved more proximate severe health consequences and death).

The Proposed Coverage Decision: CED in Certain Randomized Clinical Trials Only

CMS noted the high prevalence and heavy burden of AD on Medicare beneficiaries and caregivers. CMS further acknowledged the high unmet need for effective treatment, and recognized that there was some early but promising evidence of mAb benefit. Consequently, CMS proposed to cover FDA-approved mAbs for AD treatment under CED using RCTs that meet certain design, enrollment, and site of service criteria, and determined that "*the CED paradigm provides the most appropriate pathway to provide Medicare coverage while additional evidence is developed.*" CMS opted to provide access through RCTs, because such studies constitute the most methodologically rigorous study design to demonstrate the causal relationship between an intervention and health outcomes while minimizing bias. In addition, CMS explained, *"We have additional concerns at this time about harms in patients that would be treated outside the context of the safety monitoring of a controlled trial."* CMS further explained that a reconsideration of the final decision could be warranted after evaluating the results of the trials, including which patients showed improved health outcomes and which did not. CMS did not provide estimates of how long the process of developing, enrolling, completing, and publishing results, then reviewing and acting on the results from the desired trials, would require if the mAb treatments in development are effective. CMS acknowledged that waiting for publication and interpretation of results of an RCT would limit patient access in the interim but explained that RCTs are needed first to ensure "*appropriate access*" by demonstrating that the benefits of treatment outweigh the harms.

CED Coverage Criteria
CMS specified that covered RCTs would be required to address the following **research questions**:

- *Does use of monoclonal antibodies directed against amyloid for the treatment of AD result in a statistically significant and **clinically meaningful difference** in decline in **cognition and function**?*

  CMS reviewed the instruments used in trials with peer-reviewed results and found the most prevalently used tools to be the Alzheimer's Disease Assessment Scale-Cognitive subscale (ADAS-Cog), the Mini-Mental State Examination (MMSE), and the Clinical Dementia Rating-Sum of Boxes (CDR-SB). But CMS did not specify whether the primary endpoints of FDA-approved clinical trials, or any other particular endpoints, would be acceptable endpoints for the purpose of CMS-approved RCTs under the CED, or what level of cognitive and functional improvement would be considered clinically meaningful. Instead, CMS stated that any proposed threshold for what constitutes a clinically meaningful benefit in the CMS-approved RCTs should be supported by the published peer-reviewed literature. It provided the example of a 2019 longitudinal study that examined the minimal, clinically important difference across three AD outcome measures (CDR-SB, MMSE, and the Functional Activities Questionnaire, or FAQ) for patients on the AD continuum.[7] Investigators are given flexibility in their selection of the primary outcome in their trial protocols, but measurement instruments must have been validated through use in prior trials.

- *What are the **adverse events** associated with the use of monoclonal antibodies directed against amyloid for the treatment of AD?*

  This question is aimed at improving the understanding of the safety of AD mAbs, with a particular focus on how to better predict and avoid ARIA, and how to better manage them when they occur.

For covered RCTs, CMS highlighted the underrepresentation of patients from racially and ethnically diverse populations in clinical trials to date, and potentially significant safety risks in these and other beneficiary groups. CMS stipulated the following design criteria for study coverage:

- The **site of service** for the CMS-approved RCTs is limited to the hospital-based outpatient setting *"to ensure the highest level of clinical care, and to reassure patients that further research […] will be conducted in a rigorous setting to minimize any potential harms from the treatment."*
- The **patient inclusion criteria** are similar to those in other AD mAb trials, with a requirement that patients have a clinical diagnosis of mild cognitive impairment due to AD or mild AD dementia. Like the EMERGE and ENGAGE trials of aducanumab, patients should also have evidence of amyloid pathology consistent with AD as demonstrated by a positron emission tomography (PET) scan, or *"other evidence-based methods to detect AD pathology … if supported by the peer-reviewed, published medical literature."*
- The **diversity requirement** is important: the trial must enroll patients representative of the national population with AD. This criterion is to overcome *"the disappointing lack of inclusion of underserved populations in past trials."* CMS recognized the difficulties in achieving greater representation from these populations due to factors related to *"language, logistical barriers (e.g., time, travel), and a long-standing mistrust of the medical establishment."* In our review, none of the FDA-approved or NIH-funded trials of AD mAbs currently underway appear to meet this diversity criterion despite the higher prevalence of AD in black and non-white Americans, suggesting significant challenges in engaging sites and patient populations to achieve such diversity in AD trials.
- **One PET scan** is covered, if the trial requires a beta-amyloid PET scan, in line with CMS's existing RCT coverage for beta-amyloid PET.
- The **RCT study may be extended to a longitudinal study** after it demonstrates clinically meaningful benefits, so that coverage can continue. CMS did not clearly specify whether such a then-nonrandomized study (i.e., registry) could be expanded to additional beneficiaries. CMS also did not specify the review mechanism for confirmation that the results showed meaningful benefits.

In addition, CMS stipulated that **any NIH-funded study will meet the proposed CED requirement**, although as noted, NIH-funded trials to date generally do not meet the diversity requirements. There is no specific description of how such NIH-funded trials would be expected to contribute to addressing the gaps in evidence identified by CMS. CMS made no similar provision for CED coverage of any FDA-approved trials.

Key Issues Implied – But Not Addressed – in the Proposed Decision Memo

In addition to the key evidence questions identified by CMS for public comment, the proposed decision memo raised questions related to the major RCTs and other studies currently underway on products in the class. These include FDA-approved pivotal Phase 3 trials on multiple newer mAb products where fewer published, peer-reviewed studies exist. Additional evidence will emerge from these and other studies in the coming months and years. The proposed decision memo noted that additional evidence is needed for broader coverage under the CMS "reasonable and necessary" standard, but did not provide clarity about how all of this "evidence in process" could contribute to meeting that standard, i.e., what

additional evidence would likely be sufficient, and in particular, whether these FDA-approved studies involving thousands of early-stage AD patients would fill the critical gaps if they meet their endpoints.

CMS generally issues coverage decisions on whole classes of products and has the authority to reconsider coverage based on additional emerging evidence. In the proposed decision, CMS indicated willingness to reconsider the National Coverage Determination (NCD) based on the results of the completed CMS-approved RCTs. This raises the question of whether the results of these Phase 3 pivotal trial data could be sufficient for a significant reconsideration, either for a particular product in the class or the whole class. If meeting the endpoints in pivotal trials underway now is not likely to be sufficient for broader coverage — and it is not clear from the proposed decision whether this will be the case — then these trials should be revised or augmented to assure that AD research investments generate the most useful evidence as quickly as possible. Consequently, commenters could help CMS provide more clarity regarding whether ongoing studies and potential future CMS-covered studies could meet its AD mAb coverage standards. The final CMS NCD for this potentially important class of innovative products could provide more predictability to guide patient, clinician, and product developer expectations and thus further investments in developing evidence.

Can CMS clarify what evidence is needed for broader coverage of a particular mAb?

CMS's analysis of the evidence from all mAb treatments led to the conclusion that there is insufficient evidence to support a "reasonable and necessary" coverage determination beyond RCTs for the class now. This analysis was largely based on the peer-reviewed evidence supporting the FDA approval of aducanumab and published studies reviewing mostly older mAb candidates. While the decision memo is for the whole class of mAb treatments, the ongoing pivotal trials of different products in development will provide additional important evidence. It is possible that different mAbs may show different effects and safety profiles, or at least produce such evidence at different times and under somewhat different criteria for use. CMS did not state whether the pivotal trials currently underway could suffice for meeting the "reasonable and necessary" standard for evidence of a meaningful clinical benefit.

In particular, CMS did not state what level of cognitive and functional improvement would be considered clinically meaningful to demonstrate the effectiveness of a particular mAb, instead referencing the peer-reviewed medical literature, and one study in particular, as we noted above. It would be helpful for the final decision to provide clarification on whether the needed evidence would be provided for mAbs that meet the primary endpoints of their FDA-approved pivotal trials, or whether CMS is considering additional or different standards. Further, if the FDA trial endpoints are not sufficient, could the trials underway now be modified or augmented to serve as a basis for meeting the "reasonable and necessary" standard? If the relevance of the many ongoing RCTs that bear on FDA and CMS decisions is not clear, the value of the time, cost, and patient participation in those trials is diminished, and opportunities for developing more relevant evidence in the near future may be lost.

Additionally, CMS highlighted a meaningful commitment to increase evidence on safety and effectiveness in diverse populations in Medicare. But CMS did not address what level of statistical confidence is needed regarding the absence of a difference in benefits and risks for particular beneficiary subpopulations, and which particular subpopulations by race, ethnicity, comorbidities, or other features require such evidence development. If an FDA-approved pivotal trial underway now meets its primary endpoints, would CMS cover the treatment for all beneficiaries represented by the trial or only certain beneficiaries, or require additional RCTs? If emerging evidence shows overall benefits but suggestions of a difference in benefits across subpopulations, would Medicare cover the AD mAb treatment for the favorable groups only? CMS also did not identify any steps that it could support –

beyond the coverage of the treatment (and presumably the placebo) in the RCT — to help address a diversity requirement that appears to have been challenging to meet, given the years of effort by NIH, product developers, and FDA to increase clinical trial diversity, with limited success. Would a therapy with stronger evidence of overall benefit remain uncovered until the diversity conditions are met? Could simpler real-world studies that have the potential to include significantly larger populations and subpopulations provide evidence on such questions, even though the resulting data may be less complete or rigorous? RCTs conducted in academic centers may not sufficiently represent the early AD population or the care they will receive in conjunction with the use of a mAb treatment.

Could positive results from trials already underway, including FDA-approved pivotal RCTs and other NIH-funded studies, support a less restrictive CED requirement (if not broad coverage)?

If positive trial results are not sufficient for full coverage, is it (1) the insufficient magnitude of effect designed in the trials, (2) inadequate representativeness of the national AD population as required for CMS-approved RCTs under the CED, or both? Should positive results from any of the ongoing pivotal Phase 3 trials warrant broader CED criteria (beyond RCTs) for the individual mAb treatment?

Such CED expansion could be done in conjunction with restrictions on conditions of use to assure safety and appropriate prescribing, as real-world evidence (RWE) and prescribing experience accumulate. Limitations on use might include coverage restricted to providers that meet certain criteria for AD management capabilities, including the ability to track and manage important safety risks such as ARIA. These provider capabilities would likely involve data collection for quality of care similar to that required in a practical AD patient registry or similar real-world data (RWD) collection effort to help address important evidence issues.

CED based on RWD could augment RCT evidence that demonstrates a meaningful overall population benefit, by addressing further questions and larger and more diverse patient populations than have participated in RCTs. Such large longitudinal postmarket studies would likely be more informative than RCTs about some of the important safety questions related to the use of the mAbs, including the course and management of ARIA, other significant adverse events or complications and their management, and potential safety issues with long-term treatment. More extensive data collection could be undertaken by clinical groups that specialize in AD management, or those in integrated delivery systems that already use electronic records to track AD patients longitudinally. A less burdensome CED approach could support quality assurance as well as some evidence development through a minimal core dataset reporting, including key patient characteristics, comorbidities, and major outcomes (e.g., a periodic "mini-MoCA" test and basic reporting on major adverse events), in which a broader range of providers could participate. While a less extensive tier of data reporting would provide less detailed data, it would result in a broader and more representative evidence base on AD patients and could extend and complement evidence from RCTs and more detailed registries.

Would stronger emerging evidence from a single mAb affect coverage for the class?

We have described how significant evidence might emerge from pivotal trials underway now on particular new mAbs, and how such evidence raises questions about whether the NCD would be modified for that mAb. Alternatively, would CMS continue to consider the totality of evidence for the entire class to make coverage decisions for the whole class, rather than identifying a pathway for a particular mAb treatment to receive differential coverage? How might additional evidence relevant to potential class effects in other areas (e.g., on ARIA-related adverse events and how to manage them) lead to updates in coverage and CED requirements?

What level of evidence is required for the use of plaque reduction as a surrogate marker to meet the CMS "reasonable and necessary" standard for broader coverage?

The numerous trials of multiple AD mAbs that are currently underway will provide additional evidence relevant to determining whether plaque reduction is a valid surrogate marker for slowing cognitive decline. CMS noted FDA's conclusion that evidence was not yet sufficient for validation. However, CMS did not state whether it would accept a subsequent determination by FDA that the evidence is sufficient to consider plaque reduction to be a validated surrogate. Would FDA's conclusion about surrogate marker validation satisfy the evidence requirement for "reasonable and necessary" coverage, and if not, what additional evidence might be required? Clarity on these issues would help assure that the continuation of current trials will be done in a way that maximizes the value of evidence developed from trial participants and focuses additional evidence development.

Can CMS, FDA, and other relevant public health agencies implement a coordinated, ongoing process for timely assessment of the status of evolving evidence on mAb products and its implications for Medicare coverage in this important area of unmet medical need?

The proposed NCD reflects significant, informed input from researchers at the NIH. However, it is not clear whether CMS also benefitted from insights from other government experts in this space, particularly those at FDA. In many areas of clinical development, timely and extensive discussions between CMS and FDA expert staff have helped to address evidence relevant for coverage issues, including to support the development of additional postmarket evidence in ways that enabled more timely and somewhat broader coverage for new types of products, such as innovative new types of medical devices like transcatheter aortic valve replacements, combination products such as drug-eluting stents, and accelerated-approval cancer drugs for important unmet needs. Such interactions can be complicated by FDA's review of proprietary, commercially confidential information. However, in many cases, companies have been willing to share such information with CMS ahead of a public release when they are relevant to timely and informed coverage decisions. Moreover, many of the issues described here are *class-wide* issues related to predictable and evidence-based coverage for an innovative class of products, which can draw on public information (e.g. published details on pivotal trial designs to assess any remaining gaps) or class-related evidence that FDA has also worked to synthesize.

Conclusion

The proposed CMS NCD represents a substantial and extensive review of much of the publicly available evidence on mAb treatments for AD. Here, we have provided a summary of key issues that were included — and some that were not — with the goal of helping commenters address key questions in this important area of product development with considerable research activity underway for one of the nation's greatest areas of unmet medical need. Constructive comments will enable CMS to implement more effective policies in this challenging and important space, where transformation in therapies and in care models is badly needed. We welcome any suggestions or feedback on the issues that we have raised.

Disclosures

Mark B. McClellan, MD, PhD, is an independent director on the boards of Johnson & Johnson, Cigna, Alignment Healthcare, and PrognomIQ; co-chairs the Guiding Committee for the Health Care Payment Learning and Action Network; and receives fees for serving as an advisor for Arsenal Capital Partners, Blackstone Life Sciences, and MITRE.

References

[1] "FDA Grants Accelerated Approval for Alzheimer's Drug," Food and Drug Administration, 2021, https://www.fda.gov/news-events/press-announcements/fda-grants-accelerated-approval-alzheimers-drug.

[2] This criterion includes the duration and frequency that is considered appropriate for the item or service in terms of whether it is:

- Furnished in accordance with accepted standards of medical practice for the diagnosis
- or treatment of the patient's condition or to improve the function of a malformed body member;
- Furnished in a setting appropriate to the patient's medical needs and condition;
- Ordered and furnished by qualified personnel;
- One that meets, but does not exceed, the patient's medical need; and
- At least as beneficial as an existing and available medically appropriate alternative.

[3] "NCA - Monoclonal Antibodies Directed Against Amyloid for the Treatment of Alzheimer's Disease (CAG-00460N) - Proposed Decision Memo," CMS Medicare Coverage Database, 2022, https://www.cms.gov/medicare-coverage-database/view/ncacal-decision-memo.aspx?proposed=Y&NCAId=305.

[4] These include reports from the FDA, the Guideline Development, Dissemination and Implementation Subcommittee of the American Academy of Neurology, the National Institute on Aging, and the National Institute for Health Care and Excellence and the Institute for Clinical and Economic Review's May 5, 2021 report.

[5] Cummings J. The Role of Biomarkers in Alzheimer's Disease Drug Development. Adv Exp Med Biol. 2019;1118:29-61. doi:10.1007/978-3-030-05542-4_2.

[6] Evidence Table 2. Individual Phase 3 RCTs, and meta-analyses, of monoclonal antibodies versus placebo in Alzheimer's Disease, https://www.cms.gov/files/document/id305evtable2pdf.pdf.

[7] Andrews JS, et al. Disease severity and minimal clinically important differences in clinical outcome assessments for Alzheimer's disease clinical trials. Alzheimers Dement (N Y). 2019;5:354-363. Published 2019 Aug