January 11, 2022

Summary

Proposed Decision Memo: Monoclonal Antibodies Directed Against Amyloid for the Treatment of Alzheimer's Disease (CAG-00460N) –

On January 11, 2022, CMS released a Proposed Decision Memorandum (PDM) in its National Coverage Analysis (NCA) for "Monoclonal Antibodies Directed Against Amyloid for the Treatment of Alzheimer's Disease." This NCA was generated internally, in July 2021, and the Final Decision Memorandum is expected by April 11, 2022. Comments on the PDM are due February 10, 2022.

In the PDM, CMS focuses on the class of monoclonal antibodies (mABs), and states that based on its review of the totality of the evidence, "there is some preliminary research that shows promise, but it's far from conclusive and more rigorous individual trials (i.e., RCTs) continue to be needed to determine the clinical benefit of anti-amyloid mABs for the treatment of [Alzheimer's disease (AD)]." CMS proposes to utilize the Coverage with Evidence Development (CED) policy to restrict coverage for FDA approved mABs directed against amyloid for the treatment of AD to randomized controlled trials (RCTs) that satisfy specified coverage criteria, and trials supported by the National Institutes of Health (NIH). Additionally, the PDM provides that "[a] CMS approved randomized controlled trial may be extended to a prospective longitudinal study when the randomized controlled trial is completed, and the findings of the randomized controlled trial demonstrate a clinically meaningful benefit in cognition and function."

The PDM also provides that where trials include a beta amyloid positron emission tomography (PET) scan as part of the protocol, the scan will meet the separate CED requirements previously established in the Beta Amyloid Positron Emission Tomography in Dementia and Neurodegenerative Disease NCD (220.6.20). As a result, one beta amyloid PET scan will be covered per patient as part of the clinical trial, if the patient did not previously receive a beta amyloid PET scan.

Evidence Review

A. Scope of Evidence Review

- CMS notes that it has reviewed over 250 relevant, peer-reviewed documents, encompassing all trials of anti-amyloid drugs since 2010. In particular, the search was conducted independently and concurrently by a NIH librarian, the contractor International Consulting Associates (ICA), and CAG. Each incorporated all the distinct, relevant references into a single reference database.

- The agency concludes that "Biogen's secondary analysis cannot overturn, definitively confirm, or substitute for, the RCT evidence. With conflicting results from two RCTs (EMERGE and ENGAGE), and a secondary analysis that did not resolve the difference between the two RCTs, CMS believes that the available evidence is insufficient to establish that the treatment is reasonable and necessary under section 1862(a)(1)(A) of the Social Security Act."

  - CMS states that "[a]s of this writing, Biogen's secondary analysis has not been published in a peer- reviewed medical journal for CMS to review, nor have the original trials been published separately. We strongly encourage such publications."
  - The PDM includes two evidence tables reviewing trials of mABs other than aducanumab (available here and here).

- The agency also cites "[m]any published expert opinions and reports [that] have questioned Biogen's secondary analysis of trial data and its conclusions regarding aducanumab's effectiveness." CMS takes the position that "[m]ost experts believed there was little, if any, reliable evidence to answer the key question of clinical benefit. Some experts highlighted possible alternative explanations for why the two RCTs, EMERGE and ENGAGE, had conflicting outcomes based on a post-hoc analysis." The agency cites the following articles: Knopman 2020, Howard 2020, Lin 2021, Rubin 2021, Mullard 2021, Liu 2021, Alexander 2021, Rabinovici 2021, Karlawish 2021, Dunn 2021, FDA 2021.

  - CMS also referenced the FDA Advisory Committee's vote against recommending approval in November 2020

B. Assessment of Benefits and Harms

- The agency notes that "[d]ue to the lack of a clear clinical benefit and the frequency of adverse events like [amyloid-related imaging abnormalities] (ARIA), the evidence does not support that the benefits outweigh the harms for mAbs directed against amyloid for the treatment of AD." Noting that "[a]dverse events are more closely monitored and treated in the context of a clinical trial compared to general practice, CMS concludes that "[w]e 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 stated that "the clinical benefit of [beta amyloid] clearance remains uncertain, given that no trial has convincingly demonstrated a clinically meaningful improvement in health outcomes, such as a substantial difference in a global assessment of cognition and function (which the primary outcome for the aducanumab trials, the Clinical Dementia Rating – Sum of Boxes, or CDR-SB does) compared to a control group."

  - The agency states that "[b]ased on our review of the totality of the evidence…we agree with the NIA meta-analysis that there is some preliminary research that shows promise, but it's far from conclusive and more rigorous individual trials (i.e., RCTs) continue to be needed to determine the clinical benefit of anti-amyloid mABs for the treatment of AD."

- The PDM notes that "anti-amyloid mAb trials have demonstrated harms such as headaches, dizziness, falls, and [ARIA]. At the time of this writing, there is ongoing assessment of whether the use of an anti-amyloid mAb has caused or contributed to death."

C. Public Comments

- The PDM states that during the 30-day comment period following the release of the tracking sheet, CMS received 131 comments.

- According to the agency, of these comments, the majority of approximately 77 commenters did not support coverage or recommended CED. Twenty-six comments did not state a clear position regarding coverage.

- CMS states that the themes from the comments included "[c]riticism of the evidence for Aduhelm™, citing conflicting results between EMERGE and ENGAGE, and the presence of adverse events (e.g., [ARIA]). The commenters cited that these are reasons additional evidence is needed before the drug is coverable, or expressing that coverage should be limited to CED. Commenters also expressed concerns over the price of Aduhelm™."

- The agency notes that other commenters "stated that CMS should cover Aduhelm™, and future anti-amyloid monoclonal antibodies, based on FDA approval and because of the lack of available effective treatments for AD. Commenters specified that diagnostic tests for beta amyloid should also be included in coverage."

National Non-Coverage Outside of CED

- The PDM proposes that "[m]onoclonal antibodies directed against amyloid for the treatment of AD provided outside of the CMS approved randomized controlled trials and trials supported by the NIH are nationally non-covered." This national non-coverage is class-wide.

- CMS states that "[t]o date, no trial of an anti-amyloid mAb has confidently demonstrated a clinically meaningful improvement in health outcomes (i.e., cognition and function) for AD patients. Thus, there is insufficient evidence to conclude that the use of monoclonal antibodies directed against amyloid is reasonable and necessary for the treatment of Alzheimer's disease under §1862(a)(1)(A) of the Social Security Act."

- CMS "recognize[s] that one individual trial (EMERGE) reportedly demonstrated statistical significance of a primary health outcome in a post-hoc, secondary analysis of data for patients receiving high-dose aducanumab, important questions remain regarding the reliability of those results."

Coverage with Evidence Development

A. Randomized Controlled Trials

- CMS is proposing to cover FDA approved monoclonal antibodies directed against amyloid for the treatment of AD under CED in CMS approved RCTs and in trials supported by the [NIH].

- CMS reasons that "[e]ffective treatments [for AD] are needed, and because of the early but promising evidence and the immense burden of this devastating disease on the Medicare population, we are proposing CED to support rigorous trials to answer whether antiamyloid mAbs improve health outcomes for patients."

- Specifically, the PDM is proposing that "a trial must be a multicenter RCT, with an appropriate control representing the standard of care. This is consistent with the designs of large, pivotal Phase 3 trials for anti-amyloid mAbs, including the most recent ones for aducanumab. In addition, to ensure the CED requirements do not assume the NIH's role in fostering, managing, or prioritizing clinical trials, this CED will cover NIH-sponsored studies of anti-amyloid mAbs."

B. CED Coverage Criteria

- The PDM proposes certain specific standards and coverage criteria for CMS-approved trials. Notably, most of these standards apply only to CMS-approved RCTs, and not to trials supported by the NIH

- **Hospital Outpatient Setting.** All trials must be conducted "in a hospital-based outpatient setting." This requirement applies to CMS-approved RCTs **and** to trials supported by the NIH.

    - The PDM explains that this setting "ensures integrated and coordinated care, availability of advanced imaging or other diagnostic tests, and rapidly-available advanced care if needed."

- **Patient Criteria**

    - Patients must have 1) a clinical diagnosis of mild cognitive impairment (MCI) due to AD or mild AD dementia; and 2) evidence of amyloid pathology consistent with AD.
    - Patients may not have 1) any neurological or other medical condition (other than AD) that may significantly contribute to cognitive decline; 2) expected death from any cause during the duration of the study; or 3) medical conditions, other than AD, likely to increase significant adverse events.

- **Research Questions.** CMS approved trials must address, at a minimum, 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?
        - The agency states that it "will use the CDR-SB to exemplify what constitutes a clinically meaningful improvement in a primary outcome. As discussed before, the CDR-SB is a widely-used outcome measure

combining cognition and function globally, and was the primary outcome for the EMERGE and ENGAGE trials of aducanumab."

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

- **Diversity.** The PDM states that "[t]he diversity of patients included in each trial must be representative of the national population diagnosed with AD."

- All studies for CMS approval "must fully describe in the protocol how the [patient criteria, research questions, and diversity requirements] will be carried out."

C. Longitudinal Studies

- The agency is proposing to allow an RCT to "be extended to a prospective longitudinal study when the [RCT] is completed, and the findings of the [RCT] demonstrate a clinically meaningful benefit in cognition and function."

    - In explaining this approach, CMS "recognize[s] that waiting for published results of an RCT may limit access." The agency states that it seeks to "strike[] an appropriate balance of providing patient access while also ensuring both protections for patients from harms and the appropriate data collection and analysis to address CMS' questions to determine whether CMS should undertake an NCD reconsideration."

- The PDM specifies that "[d]etails of the prospective longitudinal study must be included in the same protocol as the [RCT]."

Beta Amyloid PET

- The PDM also addresses the key issue of coverage for a beta amyloid PET scan as part of a trial approved under this NCD.

    - Coverage for beta amyloid PET is subject to a separate NCD (section 220.6.20 of the NCD Manual), which provides coverage for a beta amyloid PET scan only through CED.

- The PDM proposes to take the approach that where a CMS-approved or NIH-supported trial includes a beta amyloid PET scan as part of the protocol, "it has been determined that these trials also meet the CED requirements included in the Beta Amyloid Positron Emission Tomography in Dementia and Neurodegenerative Disease NCD (220.6.20), and one beta amyloid PET scan will be covered per patient, if the patient did not previously receive a beta amyloid PET scan."

    - The agency notes that "[o]ne of the questions specified in the beta amyloid PET NCD for studies to address under CED is, 'Does using [beta amyloid] PET imaging in guiding patient management, to enrich clinical trials seeking better treatments or

prevention strategies for AD, by selecting patients on the basis of biological as well as clinical and epidemiological factors, lead to improved health outcomes?'" CMS takes the position that "[t]his question would be inherently addressed by any study approved under CED for this proposed decision because all approved CED studies for this current NCD on anti-amyloid mAbs must aim to determine whether the treatment improves health outcomes for a specified AD population."

- CMS notes that "the beta amyloid PET CED provides for a single lifetime use of a [beta amyloid PET] scan per Medicare beneficiary," and specifies that "[t]his NCD does not change the frequency of the single lifetime [beta amyloid] PET scan per Medicare beneficiary. Thus, if a patient received a [beta amyloid] PET scan under the beta amyloid PET NCD, they are not eligible for an additional scan for any trial approved under this NCD. However, the results of that scan may be used to determine whether the patient is eligible for a trial."

- The PDM states that "[i]n addition to [beta amyloid] PET brain scans, other evidence-based methods to detect AD pathology will be considered if supported by the peer-reviewed, published medical literature."