Via Electronic Filing to: https://www.cms.gov/medicare-coverage-database/reports/national-coverage-ncacal-status-report.aspx?ncacaldoctype=NCA&status=Open%20for%20Public%20Comment

February 10, 2022

Tamara Syrek Jensen, JD
Director, Coverage and Analysis Group
Centers for Medicare & Medicaid Services
7500 Security Blvd
Baltimore, MD 21244

Re: Proposed Decision Memo
National Coverage Analysis (NCA) for Monoclonal Antibodies Directed Against Amyloid for the Treatment of Alzheimer's Disease (CAG-00460N)

Dear Ms. Syrek Jensen:

Haystack Project appreciates the opportunity to submit its comments to the Centers for Medicare & Medicaid Services' (CMS') proposed NCA for monoclonal antibodies directed against amyloid for the treatment of Alzheimer's disease (the proposed NCA).

Haystack Project is a 501(c)(3) non-profit organization enabling rare and ultra-rare disease advocacy organizations to highlight and address systemic access barriers to the therapies they desperately need. Our core mission is to evolve health care payment and delivery systems, spurring innovation and quality in care toward effective, accessible treatment options for Americans living with rare or ultra-rare conditions. Essential to this mission is our commitment to educate policymakers and other stakeholders about the unique circumstances of extremely rare conditions with respect to product development, commercialization, and equitable access to care.

Advances in research and development such as regenerative medicine, gene therapy, and other targeted therapy innovations offer a renewed hope that a treatment could be on the horizon for any disease, no matter how rare. This sense of optimism is, however, tempered by increasing discussions about whether payers -- public and private -- will be willing and able to pay the cost of these highly-targeted treatments.

While the proposed NCA addresses new treatments for an all-too-common condition in Medicare beneficiaries, Haystack Project has serious concerns that it will, if finalized,

- Represent an unprecedented challenge to the validity of the accelerated approval process that is integral to advancing new therapies in rare diseases

- Perpetuate and exacerbate health inequities associated with race, ethnicity, and socioeconomic status

- Impermissibly substitute CMS' analysis of clinical evidence and conclusions for decisions delegated to and made by FDA, and

- Raise significant ethical concerns by conditioning coverage for on-label use of the first FDA-approved treatment with potential to mitigate disease progression on participation in CMS-directed, randomized clinical trials.

The proposed NCA represents an unprecedented challenge to the validity of the accelerated approval process.

Haystack Project understands that CMS seeks to protect the health and wellbeing of Medicare beneficiaries and ensure the long-term fiscal integrity of the Medicare program. We are also fully aware that the accelerated approval process, and its reliance on surrogate endpoints, balances uncertainties toward access, while the national coverage decision process demands relative certainty on clinical benefit. The juxtaposition between functions within the Department of Health and Human Services (HHS) – FDA's authority to balance risks and benefits of treatments based on surrogate endpoints within the statutory accelerated approval process versus CMS' coverage decision authority – creates a potentially inevitable decision between:

- Declining to initiate the NCA process for accelerated approval therapies until confirmatory trials are completed (or fail to move forward within a reasonable time period) and/or real world evidence is sufficient to evaluate clinical benefit; or

- Accepting that each new accelerated-approval treatment will, despite addressing an unmet need in a serious or life-threatening disease, fail to clear the evidentiary hurdles within the NCA process and access will be foreclosed for every Medicare beneficiary unable to absorb the financial cost of treatment.

Said another way, if FDA is authorized to base approval on a biomarker reasonably likely to predict outcomes but CMS' NCA standards require the robust data obtained through confirmatory studies, CMS can single out any, or even all, accelerated-approval treatments, subject them to the critical lens of an NCA, and predictably decline access. The proposed NCA's statement that "[m]oreover, with limited exceptions, the expenses incurred for items or services must be reasonable and necessary . . ."[1] raises significant concerns that CMS decisions

[1] Proposed LCA, Section IX. https://www.cms.gov/medicare-coverage-database/view/ncacal-decision-memo.aspx?proposed=Y&ncaid=305&doctype=all&timeframe=30&sortBy=updated&bc=20

to leverage the NCA process will be driven by treatment costs. Haystack Project believes that this is a bad public policy rationale that could disproportionately impact individuals with rare and ultra-rare conditions and deter development of new therapies. Moreover, the plain language of Section 1862 does not invite a "cost" inquiry – it precludes Medicare payment for items and services that are not reasonable and necessary.[2]

Haystack Project supports policies that work to ensure that manufacturers gaining approval for their drug products through the FDA accelerated approval pathway act diligently in completing the confirmatory post-market studies identified in their FDA approval letter. We do not believe that the proposed NCA is based on or furthers this important objective. The assumptions underlying the proposed NCA appear to be antithetical to Congress' goal of facilitating early access to promising treatments and the FDA's statutory and delegated authority to make safety and efficacy determinations based on surrogate endpoints. The key issue is not whether CMS has the authority to decide if and when a particular item or service is reasonable and necessary. That authority has been granted to HHS by statute and delegated to CMS. **The pivotal questions are (1) whether denying coverage to on-label use of drugs and biologicals marketed under accelerated approval frustrates Congress' intent in creating that pathway, i.e., to facilitate early access to promising treatments; and (2) whether one HHS agency is empowered to negate, ignore, or reverse HHS determinations made by another HHS agency pursuant to direct statutory or delegated authority.**

Implementation of the proposed NCA will likely perpetuate and exacerbate health inequities associated with race, ethnicity, and socioeconomic status.

Haystack Project and its member organizations recognize that denial of coverage does not completely foreclose patient access to treatments. Patients with adequate financial resources have always been able to access treatments that individuals relying on insurance coverage are unable to afford. Rare disease patients and their families are often forced to decide whether they can afford a non-covered but potentially promising off-label treatment regimen, and too often face the crushing reality that evolving standards of care are financially out of reach. We do not believe that the policy preferences driving the accelerated approval pathway included the possibility of real-world implementation across HHS agencies resulting in differential access with:

- economically advantaged patients achieving early access based on physician/patient decision making, and
- patients without robust financial resources relegated to serving as research subjects for whom treatment "decisions" are driven through randomization.

[2] Social Security Act, §1862(a)(1)(A) provides, in pertinent part, that "[n]otwithstanding any other provision of this title, no payment may be made under part A or part B for any expenses incurred for items or services—
(1)(A) which, except for items and services described in a succeeding subparagraph, are not reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member.

We recognize that failures in enrolling racially and ethnically diverse populations in clinical trials increases uncertainties on the subpopulation-specific benefits and risks of emerging treatments. The lack of representative clinical trial participation by people of color is driven by a complex interplay between multiple factors, including the impacts of our longstanding history of systemic racism. People of color are more likely to have significant comorbidities that preclude clinical trial enrollment and can face substantial economic challenges associated with transportation to clinical trial sites. These challenges are compounded for Alzheimer's disease studies due to caregiver participation requirements. More importantly, however, people of color have a legitimate basis for medical mistrust, particularly with respect to any appearance or perception that participation in research is forced. A government-initiated "program" conditioning coverage on research participation in a study designed to randomly withhold an FDA-approved therapy is likely to further, rather than reduce, medical mistrust.

Haystack Project is similarly concerned that the study criteria outlined in the proposed NCA will result in data on treatment use in a limited patient population, i.e., patients without comorbidities. To the extent that CMS intends that the CED study population would be the "ceiling" on future coverage, we expect that a substantial proportion of people of color would face denials in access within the CED studies and long after confirmatory studies are completed. We urge CMS to consider whether the proposed NCA will disproportionately exclude underserved populations. In addition, we suggest that CMS develop a mechanism to evaluate the extent to which there is a difference between white and non-white patient access to these treatments outside of the CED studies.

The proposed NCA impermissibly substitutes CMS' analysis of clinical evidence and conclusions for decisions delegated to and made by FDA.

Haystack Project and its member organizations strongly oppose health policies, including Medicare coverage decisions, that perpetuate and exacerbate differential access to FDA-approved treatments. We believe that, as a matter of policy, CMS should align its decisions on access to care with the intent Congress demonstrated in affirming the accelerated approval pathway. Similarly, we assert that CMS must not, as a matter of law, substitute its de novo interpretation of evidence for determinations delegated to and made by FDA.

CMS initiated the National Coverage process shortly after FDA approved Aduhelm® and focused its analysis on whether the evidence is sufficient and sufficiently conclusive to answer the primary research question: "Is the evidence sufficient to conclude that the use of monoclonal antibodies directed against amyloid for the treatment of Alzheimer's disease improves health outcomes for Medicare beneficiaries?" CMS' inevitable conclusion was that

> [t]o date, no trial of an antiamyloid 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 (emphasis added)

Haystack Project is unaware of any new drug or biological approved based on surrogate endpoints under the accelerated approval pathway for which a similar inquiry would not preclude a positive national coverage decision. In fact, the accelerated approval pathway is based on policy priorities to defer those questions and grant access while FDA-mandated post-approval studies confirm clinical benefit. Moreover, CMS' guidance on use of CED outlines a set of governing principles, including that "CED will not duplicate or replace the FDA's authority in assuring the safety, efficacy, and security of drugs, biological products, and devices."[3] The analysis within the proposed NCA moves through a progression of CMS determinations on evidence that directly negate FDA's review and evidentiary conclusions:

- FDA approval relied on surrogate endpoints related to clearance of amyloid plaques based on FDA's determination that the surrogate endpoint was likely related to clinical benefit. The proposed NCA substitutes CMS' judgment that "[t]hus, we agree with the conclusion, published by one author reviewing all the 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.'"[4]

- FDA approval based on surrogate endpoint(s) through the accelerated approval pathway are FDA determinations that a drug or biological is safe and effective for its labeled indication(s). CMS appears to view these FDA determinations as deficient from an evidentiary perspective. The proposed NCA relies on CMS' own safety and effectiveness analysis and its conclusion that "due to the lack of a clear clinical benefit and the frequency of adverse events like ARIA, the evidence does not support that the benefits outweigh the harms for mAbs directed against amyloid for the treatment of AD."

- FDA requires completion of Phase 4 confirmatory trials to establish clinical benefit, and the manufacturer has recently announced endpoints and enrollment characteristics associated with its ENVISION confirmatory study. CMS is "proposing CED to support rigorous trials to answer whether antiamyloid mAbs improve health outcomes for patients." There is no clear rationale differentiating the goals of FDA confirmatory trials with the studies CMS proposes. More importantly, CMS has not considered that its CED paradigm may frustrate and delay enrollment in manufacturer-sponsored, FDA-mandated confirmatory studies.

The draft NCA raises significant ethical concerns with respect to individuals seeking access to the first FDA-approved treatment with potential to mitigate disease progression

[3] Medicare Coverage Document - Guidance for the Public, Industry, and CMS Staff: Coverage with Evidence Development

[4] NCA - Monoclonal Antibodies Directed Against Amyloid for the Treatment of Alzheimer's Disease (CAG-00460N) - Proposed Decision Memo (cms.gov)

As CMS noted, there are no FDA-approved treatments that impact Alzheimer's disease progression, other than the recently-approved therapy that is the subject of the proposed NCA. As more fully detailed above, Haystack Project strongly opposes the proposed NCA and the precedent it will set for Medicare beneficiaries with serious conditions addressed by therapies approved through the accelerated approval pathway. To the extent the Agency determines to finalize the proposal or any other CED framework for the subject treatment(s), we urge that it prioritize beneficiary protections over its data collection interests.

CMS' granularity on clinical study requirements, including that (1) enrolled population reflects overall disease demographic; (2) participants are randomized to treatment and control arms; (3) care is delivered within the hospital outpatient setting, and (4) study sponsors exclude individuals with comorbidities that might increase risk of adverse events, ***raise concerns that CMS is, in and of itself, conducting research.*** Given that CMS will be reviewing and approving study protocols and intends to gather and review data on patient outcomes, we urge that the Agency obtain a clear and specific assessment of the ethical and patient protection concerns associated with the NCA. We believe this is particularly important given that the subject intervention is an FDA-approved treatment for a life-limiting, progressive, and ultimately fatal condition and CMS intends to condition coverage on study participation.
In addition, we suggest that CMS:

- Create an alternative coverage pathway for Medicare beneficiaries who are unable to participate in a CMS-approved clinical trial but seek coverage for use within the FDA-approved labeled indication

- Either limit CED coverage restrictions to "new starts" or articulate a clear pathway (e.g., expedited appeal) to coverage for beneficiaries who are receiving the treatment and not exhibiting significant adverse events, including beneficiaries accessing care before NCA implementation as well as individuals receiving the treatment through coverage by another payer, expanded access, or self-pay.

    - Medicare beneficiaries able to establish that the FDA-approved treatment meets "reasonable and necessary" standards for individual claim adjudication purposes[5] should not have to mount a full challenge to the NCA to achieve access.

- Ensure that all informed consent documents in connection with CMS-approved research studies clearly articulate:

    - That the FDA-approved treatment is NOT experimental or investigational

[5] Medicare Program Integrity Manual, Section 3.6.2.2 - Reasonable and Necessary Criteria. https://www.cms.gov/Regulations-and-Guidance/Guidance/Manuals/Downloads/pim83c03.pdf

- Any alternative mechanisms available for individuals to obtain access to treatment outside participation in clinical trials of FDA-approved treatments
- Whether research subjects will be able to access treatment outside the clinical trial and any longitudinal studies if the clinical trial results demonstrate improved patient outcomes
- Whether research subjects will be informed on whether they are in the active treatment or control arm of the clinical trial
- Costs, including copayment amounts, that patients will be required to pay within the clinical trial. This must include disclosure on whether subjects randomized to the control arm will be responsible for copayments associated with the FDA-approved therapy in the treatment arm
- Availability of the FDA-approved treatment for individuals unwilling to accept the risk of randomization to the control arm and able to pay for treatment
- Disclosure of research subject responsibilities, including consent to invasive and non-invasive tests and imaging studies, that are associated with data collection rather than connected to treatment monitoring

- Clearly outline the evidentiary goals of the CED construct, including the level(s) of improvement that would be considered clinically meaningful and significant

- Provide for a monitoring function over all studies to ensure that randomization of research subjects ceases when likely clinical benefit is shown. We urge CMS to set criteria that are lower than that which would be considered as clearly demonstrative of meaningful clinical benefit within the NCA context.

Conclusion

Haystack Project appreciates the opportunity to review and respond to the proposed NCA. We have significant concerns about this proposal and strongly urge CMS to reconsider its approach to evaluating emerging treatments approved through the accelerated approval pathway. Patients with rare conditions and their families rely on the hope that research and development efforts will bring treatment innovations that reduce the burden these conditions exact. The proposed NCA creates a level of uncertainty on the validity of the accelerated approval pathway upon which most rare disease treatments rely, and we believe those uncertainties will ultimately outweigh the disease severity and unmet need considerations at the heart of this FDA mechanism. This would be devastating for individuals with rare diseases who have no treatment options to reduce disease burden or slow disease progression, and for whom early access to a therapy is critical.


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