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August 11, 2021

David Dolan, MBA
Joseph Hutter, MD
Centers for Medicare & Medicaid Services
7500 Security Boulevard
Baltimore, MD 21244

RE: Monoclonal Antibodies Directed Against Amyloid for the Treatment of Alzheimer’s Disease (CAG-00460N)

Dear Mr. Dolan and Dr. Hutter,

On behalf of the Alliance for Aging Research (the “Alliance”), we appreciate the opportunity to offer comments for the Centers for Medicare & Medicaid Services (CMS) National Coverage Determination (NCD) analysis on whether Medicare will establish a national coverage policy for monoclonal antibodies (mABs) targeting amyloid for the treatment of Alzheimer’s disease. We stand ready to work with you and your colleagues to ensure that the agency’s coverage and payment policies facilitate beneficiary access to safe and effective, reasonable and necessary care, treatments, and services for Alzheimer’s disease and related dementias, as well as other chronic, serious, life-threatening, and disabling conditions.

About the Alliance

The Alliance for Aging Research is the leading nonprofit organization dedicated to accelerating the pace of scientific discoveries and their application to vastly improve the universal human experience of aging and health. The Alliance believes advances in research help people live longer, happier, more productive lives and reduce healthcare costs over the long term. For more than 30 years, the Alliance has guided efforts to substantially increase funding and focus for aging at the National Institutes of Health and the Food and Drug Administration; built influential coalitions to guide groundbreaking regulatory improvements for age-related diseases; and created award-winning, high-impact educational materials to improve the health and well-being of older adults and their family caregivers. For more information, visit www.agingresearch.org.

Overview

This NCD analysis will apply to the Food and Drug Administration (FDA)-approved mAB drug, Aduhelm, as well as future monoclonal antibodies that target amyloid. CMS has initiated its coverage decision for the mAB drug class, which encompasses several drugs in clinical development and includes molecules that have been designated with breakthrough therapy status by the FDA and could be available soon. As drugs in the class have varied target populations and may have different efficacy profiles, the Alliance believes this Medicare coverage indication should remain flexible for new entrants by harmonizing with the FDA-approved indication and cover all FDA-approved mABs, including Aduhelm, as reasonable and necessary upon FDA approval.

The FDA indication for Aduhelm was approved under accelerated approval based on reduction in amyloid-beta plaques observed in treated patients, and continued approval is “contingent upon verification of clinical benefit in confirmatory trial(s).”¹ In addition to the FDA-required a phase 4 confirmatory trial to verify the clinical benefit of Aduhelm, the sponsor will be conducting a long-term extension study and a real-world observational study. While additional data to validate the efficacy of Aduhelm is gathered through these studies, the Alliance believes that additional evidence collection through registries or clinical trials under a CMS “coverage with evidence development” (CED) requirement would be redundant and would significantly restrict beneficiary access—including to other mAB therapies in development.

More broadly, the Alliance maintains serious concerns regarding the utilization of CEDs. Because CED falls under the NCD statutory authority, there is no specific enforcement mechanism to ensure timely research reporting compliance, which results in an ad hoc process that leaves Medicare beneficiaries in a state of uncertainty regarding their treatment. The Alliance continues to urge policymakers, including in the proposed Cures 2.0 legislation, to create unique statutory authority requirements for CMS’s CED process.^{2,3} To facilitate timely beneficiary access to new treatments, devices, and care, our suggested reforms include:

- Unique CED statutory authority should require CMS to clarify what specific evidence is needed to close a CED and provide a timeline for collecting evidence. The Alliance supports the passage of the bipartisan New Opportunities for Value to Extend Lives (NOVEL) Act (S. 2416)⁴ that would update coding, coverage, and payment processes at CMS, including CED, to improve seniors’ access to life-saving medical innovations.⁵
- Unique CED statutory authority should allow CMS additional flexibility in the clinical trial data the agency accepts. Currently, NCDs require randomized clinical trials (RCTs) for study participation; and CMS may preclude potential Medicare coverage of observational studies, as well as trial designs agreed upon between sponsors and the FDA, such as a single-arm pivotal trial or a non-randomized arm within a larger study program. CMS has acknowledged that the RCT requirement could be problematic, and even unethical, in cases where the intervention has shown substantial differences in major health outcomes compared to placebo in FDA-approved trials. In its August 14, 2019, initiation of a national coverage analysis for transcatheter mitral valve repair (TMVR), the agency stated it would be “reviewing the NCD requirement for randomized controlled trials of non-FDA approved indications and considering if it should be changed to reduce burden and encourage innovation in this space.”⁶
- Unique CED statutory authority should allow CMS access to, and oversight of, all patient registry data the agency requires as part of CEDs. Specialty societies, patient advocacy organizations, and academic centers can substantially profit from running these registries by charging providers and industry annual fees. Further, they have monopolistic control over the registries and operate with very little, if any, transparency. Currently, registry sponsors: appoint the advisors that decide on the health outcomes

¹ [FDA label for Aduhelm](#) accessed from Drugs@FDA 8/9/2021.

² [Alliance Comments on 21st Century Cures Act 2.0 Draft Legislation, December 16, 2019.](#)

³ [Alliance Comments on 21st Century Cures Act 2.0 Draft Legislation, July 16, 2021.](#)

⁴ [S.2416 - NOVEL Act of 2021.](#)

⁵ [“Medicare Coverage With Evidence Development Mandate Expires After Four Years Under Senate Bill,” Pink Sheet,](#) August 3, 2021.

⁶ [National Coverage Analysis \(NCA\) Tracking Sheet for Transcatheter Mitral Valve Repair \(TMVR\) \(CAG-00438R\).](#)

information collected; own the registry data; control who can access the data; and determine what types of analyses may be conducted using the data. CMS currently has no direct access to the registry data and no enforcement authority over whether the agency’s registry-related evidence questions are answered, let alone answered within a designated period. As a result, CEDs may drag out for a decade or more with no definitive end—leaving beneficiary access hanging in uncertainty.

- Unique CED statutory authority should also allow CMS to require that patient registry stewards annually report site-specific, risk-adjusted health outcomes in open-access, peer-reviewed journal articles.

As the Alliance and our partners noted in public comments on CMS’ proposed NCDs for transcatheter aortic valve replacement⁷ and TMVR (changed in the final NCD to mitral valve TEER, transcatheter edge-to-edge repair),^{8,9} CED requirements can create unnecessary hurdles for smaller and rural hospitals and other providers, which exacerbate current access issues and disparities for minority and rural populations. We applaud CMS’ appropriate sensitivity to equity and inclusion in treatment for Alzheimer’s disease and urge the agency to make its coverage decision through a lens that prioritizes appropriate access for mAB therapies to all eligible Medicare beneficiaries.

Additionally, CMS has historically covered most FDA-approved drugs for their labelled indications automatically, even when it restricted coverage for off-label uses. Many of the proponents of a CED recommendation for mAB therapies have cited price as the main justification^{10,11,12}, but according to CMS, “[w]hen making NCDs under section 1862(a)(1)(A) of the Social Security Act, Medicare does not consider the cost of the treatment in the analysis.” We encourage CMS to issue a final NCD for mAB therapies similar to its NCD for Chimeric Antigen Receptor (CAR) T-cell Therapy (110.24),¹³ as it reflects the flexibility needed when deciding coverage for multiple drugs in a class with varied target populations, different efficacy profiles, and distinct FDA label indications.

CMS Should Provide Guidance on Coverage During the NCA Process

We further urge CMS to issue clear guidance to its Medicare Administrative Contractors (MACs) and commercial plans that mABs, including Aduhelm, will be considered reasonable and necessary upon FDA approval. Both Medicare Advantage plans and regional MACs take CMS’s lead on coverage decisions. However, many are unlikely to approve coverage for Aduhelm until CMS issues a national decision in early 2022. A July 2021 *Pink Sheet* article noted that “At least five commercial health plans, including Blue Cross and Blue Shield plans in North Carolina, Kansas, and Florida, have announced they will not cover Aduhelm because they

⁷ [Heart Valve Disease Policy Task Force comment to CMS, July 27, 2018.](#)

⁸ [Heart Valve Disease Policy Task Force comment to CMS, September 12, 2019.](#)

⁹ [Heart Valve Disease Policy Task Force comment to CMS, July 30, 2020.](#)

¹⁰ Fleming WK, Brown CR, Shrank WH, “[Costly New Alzheimer Disease Medications on the Horizon—Financing Alternatives for Medicare](#),” *JAMA Health Forum*. 2020;1(9):e201148.

¹¹ Dickson S, Killelea A, Frank RG, “[Limiting Coverage Based On Efficacy And Safety: A Path Forward For Medicare Regarding The Alzheimer’s Treatment Aducanumab](#),” *Health Affairs Blog*, June 7, 2021.

¹² Chambers JD, Lin PJ, Tunis SR, “[Medicare ‘Coverage With Evidence Development’ For Aducanumab? How Might It Work?](#)” *Health Affairs Blog*, June 30, 2021.

¹³ [National Coverage Determination \(NCD\) for Chimeric Antigen Receptor \(CAR\) T-cell Therapy \(110.24\).](#)

consider it to be “investigational.”¹⁴ The article also quoted former CMS Administrator Dr. Mark McClellan, who predicted that most regional MACs would also not approve coverage before next year, stating, “[a]ny MAC that gets a claim in their region can cover it or not, based on their own processes. But my sense is that most are basically saying ‘no’ and if you are a physician and submit a claim and the Medicare MAC says, ‘we haven’t gotten direction from CMS,’ that means ‘no.’”

Unless CMS provides guidance to Medicare Advantage plans and MACs regarding coverage during its NCA process, it is likely that only patients who have the resources to pay the total cost of the drug and accompanying administration fees will be able to access it. The health equity disparity referenced above would only be exacerbated. The Alliance encourages CMS to pursue its public health mission, follow the FDA’s approval decision, and issue interim coverage guidance with the sponsor that will apply to the NCA period.

The Importance of Alzheimer’s Disease Imaging Diagnostics

Patients are currently assessed for Alzheimer’s disease in the clinical setting based on their symptoms. It is typically a diagnosis of exclusion, where other potential causes for memory problems are ruled out first. Prior to positron emission tomography (PET) imaging, a definitive diagnosis of the disease could only be made by examining brain tissue post-mortem for the presence and distribution of both amyloid-beta plaques and tau neurofibrillary tangles. With the availability of FDA-approved amyloid and tau radiopharmaceuticals, which bind to amyloid plaques and tau tangles, evaluation through PET imaging has significantly helped in the diagnosis and staging of Alzheimer’s disease as well as in identifying which patients may benefit from treatment.

While amyloid and tau PET scans are FDA-approved for clinical use, they are not generally covered or reimbursed by CMS. In 2013, Medicare decided to strictly limit coverage of amyloid PET imaging under CED, citing insufficient evidence that the imaging would make a difference for patients with a disease with no cure and limited symptomatic treatment.¹⁵ As part of its published appropriate use criteria, CMS required that 1) knowledge of amyloid PET results was expected to change diagnosis and management and 2) whether amyloid PET is associated with improved clinical outcomes.

To address whether amyloid PET results were expected to change diagnosis and management, the Imaging Dementia-Evidence for Amyloid Scanning (IDEAS) study ran from February 2016 to December 2017. The study involved more than 18,000 Medicare beneficiaries with mild cognitive impairment or dementia who underwent amyloid PET to determine if their brains contain the amyloid plaques associated with Alzheimer’s disease.¹⁶

¹⁴ [“Medicare Coverage For Aduhelm Conditioned On Randomized Trial Would Be ‘Unusual’ – McClellan” Pink Sheet, July 16, 2021.](#)

¹⁵ [Centers for Medicare & Medicaid Services. Decision memo for beta amyloid positron emission tomography in dementia and neurodegenerative disease \(CAG-00431N\).](#)

¹⁶ Rabinovici GD, Gatsonis C, Apgar C, et al., [“Association of Amyloid Positron Emission Tomography With Subsequent Change in Clinical Management Among Medicare Beneficiaries With Mild Cognitive Impairment or Dementia.” JAMA 2019;321\(13\): 1286-1294.](#)

Although a positive test for amyloid plaques does not definitively mean someone has Alzheimer’s disease, importantly, *a negative result rules the disease out*. The IDEAS data analysis, published in *JAMA* in April 2019, found approximately 36 percent of patients clinically diagnosed with Alzheimer’s disease and 61 percent of patients with mild cognitive impairment (MCI) were *negative* for amyloid plaque by amyloid PET scan.¹⁷ These PET results profoundly impacted the primary study endpoint, which was the post-PET care management plan. More than 60 percent of study participants in both the MCI and dementia patient groups *had changes in care plans post-PET, most notably in the starting, stopping, or modification of Alzheimer’s disease drug therapy*, but also in the use of other drug therapy and/or counseling about safety and future planning. Additionally, physicians reported that PET results contributed substantially to the post-PET management plan in 85.2 percent of instances in which a change was made, further validating the usefulness of the diagnostic.¹⁸ Therefore, PET scans had a direct impact on changing patient diagnosis and management.

Eight years ago, when CMS finalized its amyloid PET NCD for dementia, there were no FDA-approved disease-modifying therapies (DMTs) for Alzheimer’s disease. In the absence of effective dementia therapies, it was postulated that amyloid PET would need to show significant changes in dementia diagnosis and management and demonstrate improved clinical outcomes compared to those beneficiaries with dementia who had not undergone amyloid PET. These latter, claims-based analysis results are not yet published, so CMS has delayed closing this CED and has not responded to requests to open a reconsideration. Now that a presumed disease-modifying mAB therapy has recently received FDA accelerated approval, CMS should end its NCD for amyloid PET under CED and transition it to an NCD with coverage to FDA-approved label.

Additionally, in May 2020, the FDA approved the first radiopharmaceutical for PET imaging of tau tangles for use in adults with cognitive impairment who are being evaluated for Alzheimer’s disease. However, tau PET was not covered by Medicare after its FDA approval due to preamble language included under section 220.6 of CMS’ NCD Manual that states, “a particular use of PET scans is not covered unless this manual specifically provides that such use is covered.” Fortunately, in the CY 2022 Physician Fee Service Proposed Rule¹⁹, CMS proposes retiring section 220.6’s language, which the Alliance supports.

The ability to test the accumulation and distribution of amyloid and tau tangles in the brain will aid diagnosis and ultimately help physicians make more informed decisions about patient care, including whether to treat with mABs. The time is now for CMS to broaden coverage and access.

Equity and Inclusion Considerations

According to the National Institute on Aging (NIA), older Black Americans and Hispanic Americans are disproportionately affected by Alzheimer’s disease and other dementias compared to older white Americans.²⁰ Genetic factors do not account for these differences. The difference in risk for Alzheimer’s disease and other

¹⁷ Ibid.

¹⁸ Ibid.

¹⁹ [Medicare Program; CY 2022 Payment Policies Under the Physician Fee Schedule and Other Changes to Part B Payment Policies; Medicare Shared Savings Program Requirements; Provider Enrollment Regulation Updates; Provider and Supplier Prepayment and Post-Payment Medical Review Requirements](#).

²⁰ National Institute on Aging (NIA), National Institutes of Health (NIH). [Alzheimer’s Disease Fact Sheet](#). Content reviewed July 2021.

dementias is explained by negative social determinants of health for older Black and Hispanic populations compared with older white populations. Chronic health conditions associated with higher dementia risk, such as cardiovascular disease and diabetes, disproportionately affect Black and Hispanic populations.²¹ Social and environmental disparities, including lower levels and quality of education, higher rates of poverty, and greater exposure to adversity and discrimination, increase the risk for these chronic conditions and risk for dementia in Black and Hispanic populations.²²

A recent analysis by UsAgainstAlzheimer’s and the Urban Institute found that U.S. counties with the highest prevalence of Alzheimer’s disease among Black and Hispanic Americans in the Medicare program tend to have worse socioeconomic conditions than counties with the lowest prevalence of Alzheimer’s.²³ Families living in these counties were less likely to have health insurance, less likely to have access to exercise opportunities, and less likely to have a bachelor’s degree or higher. They were also more likely to have lower incomes and report poorer health than families living in counties with lower levels of Alzheimer’s disease.

Additionally, health disparities in Alzheimer’s disease detection and treatment for communities of color remain unaddressed. Patients of color are far less likely to have the condition diagnosed²⁴ and less likely to be referred to dementia specialists.²⁵ The underrepresentation of minorities in Alzheimer’s disease research also raises serious concerns. For example, Black patients with Alzheimer’s disease may have lower tau tangles levels than non-Hispanic White patients,²⁶ which poses a risk of false-negative diagnosis and underestimated staging for Alzheimer’s disease among Black patients. The safety and efficacy of new Alzheimer’s disease treatments in minority populations is unknown, given how few have participated in clinical trials. FDA-required post-market studies for Aduhelm, and future mAB therapies, must address these gaps.

The Alzheimer’s Association’s 2021 *Special Report: Race, Ethnicity, and Alzheimer’s in America*, found that many Alzheimer’s patients and caregivers of color state that racism is a barrier to getting adequate care. According to the report, 66 percent of Black Americans surveyed believed discrimination made it harder for them to access good care for Alzheimer’s; and about 40 percent of Hispanic and Native American people reported the same barriers.²⁷ The discrimination included providers not listening to patients or caregivers of color, talking down to them, and treating them rudely. The report states that “All of this points to a need for health disparities research that employs life course perspectives to account for the many environmental and sociocultural factors that may put disproportionately affected populations at increased risk for Alzheimer’s and other dementias.”²⁸

²¹ Lines LM, Sherif NA, Wiener JM. [Racial and ethnic disparities among individuals with Alzheimer’s disease in the United States: A literature review](#). Research Triangle Park, NC: RTI Press; 2014.

²² Weuve J, Barnes LL, Mendes de Leon CF, Rajan KB, Beck T, Aggarwal NT, et al. [Cognitive aging in black and white Americans: Cognition, cognitive decline, and incidence of Alzheimer disease dementia](#). *Epidemiology* 2018;29(1):151-9.

²³ [Place & Brain Health Equity: Understanding the County-Level Impacts of Alzheimer’s](#).

²⁴ https://www.alz.org/aaic/downloads2020/2020_Race_and_Ethnicity_Fact_Sheet.pdf

²⁵ Landon BE, Onnela JP, Meneades L, et al, “[Assessment of Racial Disparities in Primary Care Physician Specialty Referrals](#),” *JAMA* 2021;4(1):e2029238.

²⁶ Morris JC, Schindler SE, McCue LM, et al. “[Assessment of racial disparities in biomarkers for Alzheimer disease](#),” *JAMA Neurol* 2019;76:264-273.

²⁷ [2021 Alzheimer’s Disease Facts and Figures](#), Alzheimer’s Association, March 2, 2021.

²⁸ *Ibid*.

Alliance for Aging Research

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

The Alliance cautions CMS not to inadvertently contribute to and exacerbate the massive racial and ethnic inequalities in access to Alzheimer's disease detection and treatment with a CED decision that will layer on additional clinical studies, with strict coverage requirements for sites of care and types of specialists, and/or mandate the collection of health outcomes through burdensome patient registries that may either duplicate planned sponsor studies or take longer to complete. If nothing else, we strongly urge CMS not to use "lack of evidence on minority populations" as part of the rationale to establish a coverage policy that will likely restrict access to those very same populations who have the highest need.

Conclusion

While the Alliance supports CMS' consideration of Medicare coverage for mAB therapies targeting amyloid for the treatment of Alzheimer's disease, we recognize the complexities of opening a coverage decision for the drug class. Additionally, we continue to have serious concerns regarding the utilization of CEDs in the absence of unique statutory authority requirements for CMS' CED process. Given the additional FDA study requirements to validate the efficacy of Aduhelm and other molecules in the class that will be subject to similar mandates, the Alliance does not believe CMS should initiate additional evidence collection through registries or clinical trials under CED. CMS' Medicare coverage decision for mAB therapies targeting amyloid for treating Alzheimer's disease should remain flexible by harmonizing with the FDA-approved indication and cover all FDA-approved mABs as reasonable and necessary upon FDA approval.

Thank you for considering our views and for CMS' commitment to improved detection of and quality care for people with Alzheimer's disease. If you have questions for our organization, please do not hesitate to contact me at speschin@agingresearch.org or the Alliance's Manager of Public Policy, Ryne Carney, at rcarney@agingresearch.org.

Sincerely,

A handwritten signature in cursive script that reads "Susan Peschin".

Susan Peschin, MHS
President and CEO