



February 10, 2022

BY ELECTRONIC DELIVERY

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

Executive Summary

Biogen, Inc. (Biogen) appreciates the opportunity to comment on the proposed national coverage determination (NCD) for monoclonal antibodies directed against amyloid for the treatment of Alzheimer’s disease (CAG-00460N).¹

The introduction of amyloid-directed monoclonal antibody therapies (mAbs) heralds a new, exciting era for the Alzheimer’s disease community. The Food and Drug Administration’s (FDA’s) approval of ADUHELM[®] (aducanumab-avwa) is the first approval in almost two decades of a new treatment for Alzheimer’s disease. ADUHELM provides a first-ever option to treat the underlying pathology of this disease, and we are committed to constructively engaging with the Centers for Medicare & Medicaid Services (CMS) to

¹ CMS, Proposed Decision Memo: Monoclonal Antibodies Directed Against Amyloid for the Treatment of Alzheimer’s Disease (CAG-00460N), January 11, 2022, NCA - Monoclonal Antibodies Directed Against Amyloid for the Treatment of Alzheimer’s Disease (CAG-00460N) - Proposed Decision Memo ([cms.gov](https://www.cms.gov)). (“Decision Memorandum”).

ensure appropriate access for patients to this novel FDA-approved therapy and others that may follow.

As is the case with any new medical innovation, we agree that ongoing data generation should continue to characterize the benefit-risk profile for this class of therapies. Specifically, we agree that there is a need for large scale real-world data generation to answer questions about efficacy and safety of amyloid-directed mAbs outside of a randomized controlled trial (RCT).

Biogen is strongly committed to continued evidence-generation, as has been our customary practice in other therapeutic areas. The most appropriate path forward is one that supports a range of real-world evidence (RWE) generation efforts that can address the questions identified in the proposed NCD and provide expanded evidence including patient and caregiver reported outcomes. As discussed with agency policymakers, we propose a three-pronged approach to RWE generation that would complement rather than duplicate existing RCTs, and answer CMS' remaining questions:

- **A focused registry, such as the International Collaboration for Real-World Evidence in Alzheimer's Disease (ICARE AD) to measure real-world outcomes,**
- **A novel Alzheimer's Disease Clinical Data Research Network (CDRN), modelled on approaches from other diseases like MS and oncology to allow for broad data-sharing and comparative analyses, and**
- **Prospective studies of Medicare claims, to better understand utilization patterns (including demographic and geographic differences).**

Applying a coverage with evidence development (CED) policy would significantly limit and delay coverage for the class, as well as create a major burden for providers, patients, and CMS. By doing so, this proposal, or any other CED, would unintentionally undermine generation of new data – the opposite of CMS' stated intent. In other words, generating RWE will only be possible if CMS provides coverage for ADUHELM (and other amyloid-directed mAbs, as they are approved by FDA) outside of a CED paradigm.

For these reasons, and those set forth below, Biogen disagrees with any application of CED in this case.

- **In contradiction to the FDA's determination of safety and efficacy, CMS' proposal to apply a restrictive CED policy denies access to ADUHELM, the only FDA-approved treatment for Alzheimer's disease in 20 years, and the entire class of therapies for the vast majority of beneficiaries with early Alzheimer's disease.**

- The proposed NCD mischaracterizes existing evidence on amyloid-directed mAbs, and ADUHELM specifically, in a manner that is inconsistent with FDA’s findings and contemporary scientific understanding.
- The proposed NCD contradicts the clinical expertise of the FDA and sets an inappropriate precedent that would delay access to future Alzheimer’s disease therapies.
- CED will impair equitable access to clinically appropriate Alzheimer’s disease care and exacerbate disparities in diagnosis and treatment of Alzheimer’s Disease.
- Any application of coverage with evidence development would duplicate investigative efforts, delay access to treatment, and create a significant burden on providers and patients.

As such, we respectfully urge CMS to align Medicare coverage for the class of amyloid-directed therapies with the FDA-labeled indications of individual products, consistent with the populations studied in the respective registrational clinical trials and guided by expert recommendations for clinical practice.

* * *

Comments

- A. Biogen is strongly committed to continued evidence-generation, as has been our customary practice in other therapeutic areas. The most appropriate path forward is one that supports a range of RWE generation efforts that can address the questions identified in the proposed NCD. These approaches are only viable if paired with full coverage for FDA-approved agents in the class.**

Until recently, Alzheimer’s disease medications were limited to modest, short-term symptomatics. The emerging class of amyloid-directed mAbs modify the underlying disease pathology, so that long-term, truly meaningful benefits may be possible. This is a new chapter in the history of Alzheimer’s disease, where a key objective of care should be alleviating the day-to-day burden on patients and caregivers.

Additionally, real-world studies include larger patient populations that are historically underrepresented in RCTs (e.g. patients who are ethnically/racially/geographically diverse, have comorbid conditions, are taking concomitant medications, etc.) and thus mitigate the potential external validity issues that RCTs suffer from when there is limited applicability of RCT results to other

populations, settings, treatment regimens and outcomes.² Recommendations of use for ADUHELM can be adjusted to ensure patient safety and optimization of effectiveness.

1. *RWE would capture a holistic view of the patient journey inclusive of care provided in a variety of settings.*

Many of the trial sites for ADUHELM, as well as for other amyloid-directed mAbs are not hospital-based outpatient settings, but include infusion centers, private practices, and medical research centers. Unlike RCTs, the resulting RWE can inform the evolution of evidence-based clinical practice in Alzheimer's disease.

As different modalities of data collection vary in the depth of clinical information and the breadth of patient representation, a single data source is unable to provide a comprehensive understanding of the patient journey across various settings of care with all the outcomes needed to evaluate disease progression and treatment outcomes.

2. *Biogen is committed to partnering with established and emerging research stakeholders in three multi-modal, real-world research initiatives, which together provide insights into the Alzheimer's disease patient's journey and the safety, effectiveness, and value of ADUHELM.*

i. **International Collaboration for Real-World Evidence in Alzheimer's Disease (ICARE AD): A Real-World Product-Specific Registry.**

Last year, Biogen launched the International Collaboration for Real-World Evidence in Alzheimer's Disease (ICARE AD), the first registry that will track cognitive and functional outcomes, identify any serious adverse events, and characterize ARIA frequency and severity in patients on ADUHELM in a real-world setting.³ This prospective, observational study will evaluate the long-term meaningful clinical and quality of life outcomes of patients with Alzheimer's disease treated with ADUHELM in the real-world setting, as well as provide insight into the health care resource utilization of Alzheimer's disease patients and the burden placed on informants and care partners. The study will assess the long-term safety outcomes of ADUHELM by capturing adverse events, including serious adverse events and the incidence of ARIA and any related adverse events over the long-term. As expected in real-world practice, the diagnosis of MCI or mild dementia stages of Alzheimer's disease,

² Rothwell P. M. (2006). Factors that can affect the external validity of randomised controlled trials. *PLoS clinical trials*, 1(1), e9. <https://doi.org/10.1371/journal.pctr.0010009>.

³ Galvin J, et al. ICARE AD-US: Design of a Prospective, Single-Arm, Multicenter, Noninterventional Real-World Study of Aducanumab in the United States. Oral presentation at AAIC 2021.

treatment dose regimen, and routine MRI monitoring will follow the Prescribing Information,⁴ and all activities related to patient management will be conducted according to the site investigator’s clinical judgment. Follow-up visits will occur approximately every 6 to 12 months and per the investigator’s clinical judgment for up to 5 years. All adverse events, including ARIA detected on scheduled monitoring MRI scans or unscheduled scans, any symptoms, and their severity will be recorded and reported by the Biogen Pharmacovigilance team per FDA requirements.

This study aims to enroll approximately 6,000 patients with early-stage Alzheimer’s disease from approximately 200 sites in the United States. Importantly, and as recently recommended in multiple stakeholders’ responses to the draft NCD, these sites will include both hospital and non-hospital-based study sites. Clinical outcome measures include cognitive, functional, and behavior scales used in research and practice. All patients will have a diagnosis of MCI or mild dementia stages of Alzheimer’s disease, as confirmed by clinical evaluations and an amyloid biomarker test. Importantly, understanding the clinical meaningfulness of a treatment must go beyond biomarkers and cognitive and functional changes, and include the patient and care partner relevance of these benefits. This study will focus on patient-centric clinically meaningful outcomes by capturing several patient-reported outcomes (PROs), including quality of life, care partner burden, and patient and care partner global impression of health over time.

As a treatment registry, ICARE AD provides RWE on ADUHELM alone, to study long-term safety and clinically meaningful effectiveness using cognitive and functional measures. ICARE AD can be integrated with or embedded in larger evidence generation initiatives providing opportunities to study comparative effectiveness using broader patient populations. These initiatives may include a research network (CDRN), described below, and the planned Alzheimer’s Association’s registry, Alzheimer’s National Registry for Treatment and Diagnostics (ALZ-NET).⁵ Lastly, ICARE AD may serve as a model for incorporating future treatment registries.

ii. Clinical Data Research Network (CDRN): A Decentralized Prospective Observational Disease-Specific Study.

Biogen is a recognized leader in real-world evidence generation with a successful history in multiple sclerosis⁶ and spinal muscular atrophy.⁷ Biogen

⁴ADUHELM [Prescribing Information]. Cambridge, MA: Biogen, June 2021.

⁵Alzheimer’s Association. Alzheimer’s Association Announces National Effort to Collect “Real World” Data on Newly-Approved Treatments. November 9, 2021. <https://www.alz.org/news/2021/alzheimers-association-announces-national-effort>.

⁶Hersh CM, et al. Impact of natalizumab on quality of life in a real-world cohort of patients with multiple sclerosis: Results from MS PATHS. *Multiple Sclerosis Journal. Experimental, Translational and Clinical*. 2021 April;1-13. doi:10.1177/20552173211004634

⁷Johnson NB, et al. Characterization of Adult Patients with SMA Treated in US Hospital Settings: A Natural History Study in the Premier Healthcare Database. *Journal of Neuromuscular Disease*. 2021 April 3;8:569-578.

established MS PATHS (Multiple Sclerosis Partners Advancing Technology and Health Solutions) six years ago to generate deeper data than a standard observational study. MS PATHS is a clinical data research network (CDRN) of 10 globally leading MS Centers following a cohort of 20,000 patients. Our long experience with MS PATHS has proven that CDRNs relying on shared access to high-definition real-world data is a prerequisite to generate robust RWE that may enable a Learning Health Ecosystem to be sufficiently robust and impactful on clinical research and patient care.⁸

Biogen plans to initiate a 5-plus year decentralized prospective observational Clinical Data Research Network (CDRN) study of over 50,000 patients (including a voluntary diversity target) with biomarker confirmed MCI and mild dementia stage of Alzheimer’s disease, including untreated patients and those treated with amyloid-directed therapies.

Our vision is to co-create a decentralized CDRN in partnership with leading Alzheimer’s disease research institutions enabled by technology to advance science, personalized medicine, and real-world evidence. Based on our experience with the MS PATHS initiative, we are hoping to be able to collaborate with some of the same Academic Centers, as the infrastructure and platforms needed for this type of CDRN approach are already in place. For the primary network, Biogen hopes to enroll approximately 5,000 patients and collect standardized, multimodal data covering at-home and in-clinic Patient Reported Outcomes (PRO), eClinical Outcome Assessments (eCOA), Electronic Medical Record (EMR) data integration, Digital Cognitive testing, standardized imaging, and (opt-in) bio-samples. The primary network would consist of a nucleus of leading members of the scientific consortium. In addition, to ensure a diverse population representative of the Medicare population, the network will incorporate an additional 100+ sites with lighter data collection on an additional 45,000 patients. We believe it is key to include centers with this simpler model to ensure the network reflects the standard of care inclusive of all Alzheimer’s disease clinics. CDRNs have supported research innovations in Alzheimer’s disease historically, including the development of a robust and consistent understanding of the natural history of disease (i.e., Alzheimer’s Disease Neuroimaging Network – ADNI)^{9,10,11} and inclusion of the patient voice in the research setting (i.e., Accelerating Data Value Across a National Community Health Center Network – ADVANCE).¹²

⁸ Mowry EM, et al. Harnessing Real-World Data to Inform Decision-Making: Multiple Sclerosis Partners Advancing Technology and Health Solutions (MS PATHS). *Front. Neurol.* 2020 August 07;11:1-15. doi: 10.3389/fneur.2020.00632.

⁹ Veitch DP, et al. Using the Alzheimer’s Disease Neuroimaging Initiative to improve early detection, diagnosis, and treatment of Alzheimer’s disease. *Alzheimer’s Dement.* 2021 Sept 28; Epub ahead of print. doi: 10.1002/alz.12422.

¹⁰ Weiner MW, et al. Impact of the Alzheimer’s Disease Neuroimaging Initiative, 2004 to 2014. *e.* 2015 July; 11(7):865-884. doi:10.1016/j.jalz.2015.04.005.

¹¹ Petersen RC, et al. Alzheimer’s Disease Neuroimaging Initiative (ADNI) Clinical Characterization. *Neurology.* 2010 Jan;74(3):201-209. doi:10.1212/WNL.0b013e3181cb3e25

¹² Warren NT et al. Building Meaningful Patient Engagement in Research: Case Study from ADVANCE Clinical Data Research Network. *Med Care.* 2018, 56 (Suppl 10 Suppl 1): S58-S63.

The intent of CDRNs is to give researchers access to a large, high definition, multi-modal, research-grade dataset. Data will be collected per standard routine clinical practice (e.g., 6-monthly in-clinic and/or remotely), including cognition/global function and biomarkers (biological and imaging), and from study-specific patient and care partner surveys, self-administered digital cognitive batteries, and a biobanking protocol. New digital health technology tools will be leveraged to enable at-home eCognitive assessments, which will be evaluated at scale for predictive, diagnostic, or prognostic purposes. Using a comprehensive clinical and biomarker-based RWE, such a CDRN will also enable Comparative Effectiveness & Safety research on amyloid-directed mAbs (as well as the standard of care), and deepen understanding of disease mechanism, trajectory, and treatment response.

As it is central to our approach to think of and catalyze interoperability with all other synergistic efforts towards the vision of a true Alzheimer's disease RWE-enabled Learning Health Ecosystem, we aim to ensure standard common data dictionaries with other RWE generation efforts (e.g., Alzheimer's Association National Registry for Treatment and Diagnostics, ALZ-NET) and SoC measures. Biogen and all network investigators each will have a copy of data with full rights to generate evidence, and we are committed to designing data access and governance principles to make this CDRN open to be joined by other research partners. We believe this will meaningfully contribute to other initiatives and stand ready to collaborate with the UsAgainstAlzheimer's Alzheimer's Disease Evidence Accelerator (ADEA) initiative across public and private stakeholders, now in early stages of development, to define and use common standards in protocols and data management that will help in shaping this foundation for future research.

The CDRN will provide a collaborative, scalable mechanism for studying safety, treatment effectiveness, and the long-term impact of new, potentially disease modifying therapies.

iii. Medicare Claims Analyses: Real-World Data to Inform Identification, Diagnosis, and Management of Alzheimer's Disease.

Claims analyses provide a rich source of data that offers a comprehensive view of a patient's journey through the entire health care system. They contain longitudinal, patient-level data capturing diagnoses, healthcare resource utilization, prescription dispensing, and adverse event information for nearly 63 million people in the United States. Medicare claims data captures this information in a standard set of pre-established codes that describe medical procedures, diagnoses, and drugs and stores them in a database that lends itself well to big data analytics. Furthermore, claims data overcome the limitations of single-site-sourced data by collecting clinical and resource utilization data across outpatient visits, inpatient admissions, ER visits,

pharmacy utilization and so on, and thus, provide a unique and powerful tool for gaining insights into the patient journey across all settings of care, and with a more representative patient population.

Medicare claims data is routinely used for a variety of scientifically rigorous research projects and the Research Data Assistance Center (ResDAC) can provide access to CMS' secure virtual data environment (VRDC) and all relevant research identifiable files. Medicare fee-for-service files are updated quarterly, which is the cadence with which we propose conducting interim analyses. This dataset is particularly useful for gaining insights regarding safety and appropriate use of amyloid-directed mAbs. For example, ARIA will be identified through the development of a reliable, claims-based algorithm leveraging a combination of diagnosis codes, medications used, and healthcare utilization. Additionally, claims data will include information about the frequency of MRI monitoring during the titration period, dosing, and discontinuation of treatment, hospitalizations and emergency department visits, and mortality. Length of hospital stay, 30-day hospital readmissions, and concomitant medication use will help characterize the severity of adverse events. Data regarding prescriber and facility characteristics will generate patient evidence that can inform improvements in the identification, diagnosis, and management of Alzheimer's disease. A claims-based approach will facilitate a rapid capture of the most serious adverse events at scale, to inform the FDA, CMS, clinicians, patients, and sponsors of emerging serious adverse events.

Claims-based data will enrich treatment and disease-related information by incorporating data from much larger population of patients and automatically broadening the demographic profile of the study population.

3. *Commitment to and importance of real-time data access and sharing.*

Taken together, we believe that these RWE efforts will conclusively address any remaining questions that CMS and the broader community have about the effectiveness and safety of ADUHELM and other amyloid-directed mAbs. For all the approaches outlined above, Biogen is committed to sharing both the data and analysis thereof with the relevant agencies, including CMS, FDA, and NIH, on an ongoing and regular basis.

Our emphasis on RWE is consistent with calls for leadership and coordinated action in accordance with principles outlined in 2016 by senior officials from FDA, CMS, NIH, AHRQ, Department of Veterans Affairs and other health agencies.¹³ All of these data generation efforts are intrinsically adaptable to address the questions and

¹³ US Food and Drug Administration. 21st Century Cures Act. Updated March 29, 2018, <https://www.fda.gov/regulatoryinformation/lawsenforcedbyfda/significantamendmentstothehdact/21stcenturycuresact/default.htm>.

needs of the new treatment environment in Alzheimer’s disease and all these efforts will ultimately help develop the treatment and research ecosystem. The necessary evolution of evidence generation **from diverse populations in a clinical practice setting**, at scale for the class of amyloid-directed mAbs therapies would be compromised by a CED policy and would **undermine these efforts, because of the delays, coverage limitations and significant patient and provider burden associated with this coverage mechanism, as described later in this letter.**

B. In contradiction to the FDA’s determination of safety and efficacy, CMS’ proposal to apply a restrictive CED policy denies access to ADUHELM, the only FDA-approved treatment for Alzheimer’s Disease in 20 years, and the entire class of therapies for the vast majority of beneficiaries with early Alzheimer’s disease.

1. Restricting coverage to beneficiaries enrolled in randomized controlled trials denies almost all Medicare beneficiaries access to ADUHELM—the only FDA-approved treatment for Alzheimer’s disease in nearly 20 years.

The CED proposal would limit coverage of ADUHELM and all subsequently approved amyloid-directed mAbs to a tiny fraction of patients with Alzheimer’s disease and would inappropriately deny Medicare beneficiaries the choice to access an FDA-approved treatment. Alzheimer’s disease is a progressive disease, and delays in access are highly detrimental to patients. Each day, hundreds of patients progress from mild cognitive impairment (MCI) or mild dementia stages of disease, underscoring the urgent need for access to treatment.¹⁴ It is, therefore, critical that therapy be available to appropriate patients in the early stage of their disease to have the optimal potential for slowing disease progression. ADUHELM is the first novel therapy approved for Alzheimer’s disease since 2003, and, until ADUHELM, there has been no approved treatment that targets the underlying pathophysiology of Alzheimer’s disease.¹⁵ Biogen disagrees with the application of any CED to ADUHELM or any FDA-approved product in the class.

2. Initiating studies to meet a CED requirement would take significant time and would delay access to care.

Practically speaking, implementing a CED-compliant RCT of the complexity contemplated by the proposed decision could take years. Even after a final NCD is

¹⁴ Gillis C, et al. Urgency to treat before it’s too late: Daily transitions to mild or moderate Alzheimer’s disease dementia in the US and Europe [Poster]. Clinical Trials in Alzheimer’s Disease (CTAD), November 9-12, 2021. Boston, MA.

¹⁵ FDA. FDA’s Decision to Approve New Treatment for Alzheimer’s Disease. June 7, 2021. <https://www.fda.gov/drugs/news-events-human-drugs/fdas-decision-approve-new-treatment-alzheimers-disease>.

issued, there would still be a need to conceptualize a study design, develop a protocol, coordinate among potential study collaborators, align with and obtain approval from CMS, obtain Institutional Review Board (IRB) approval, develop study infrastructure, recruit sites and study investigators, and then implement the study itself. For example, the Imaging Dementia-Evidence for Amyloid Scanning (IDEAS) study, the primary CED study for the Amyloid Beta Positron Emission Tomography (PET) CED requirement, took more than two years to begin enrollment after the final NCD was published by CMS,^{16,17} even though this was a far simpler registry study. Between finalization of the NCD and implementation of the studies, all Medicare beneficiaries would be denied coverage, including patients currently receiving therapy with ADUHELM.^{18,19}

3. *Even after the studies are implemented, coverage of ADUHELM or other later-approved therapies will be severely restricted to only a tiny number of eligible beneficiaries randomized to the treatment arm of CED-compliant RCTs.*

CED studies typically have limited enrollment and restrictive inclusion/exclusion criteria. For example, enrollment in the original IDEAS registry was capped at approximately 18,000 patients from February 2016 to December 2017.²⁰ The follow-up IDEAS registry, NEW IDEAS, is expected to enroll only 7,000 patients.²¹ RCT enrollment tends to be even more limited, usually to a few thousand patients. Moreover, by definition, the RCT denies treatment to those randomized to the control or placebo arm of the study. As such, this proposal will effectively impose a non-coverage decision on all Medicare beneficiaries except for the 1,000 – 2,000 patients randomized to the treatment arm of a trial. Because of the progressive nature of the disease, no other current MCI and Mild Alzheimer’s disease patients would ever be able to access treatment – they would all have progressed out of the treatment window by the time this RCT is complete.

¹⁶ ClinicalTrials.gov. Imaging Dementia-Evidence for Amyloid Scanning (IDEAS) Study. April 20, 2015.

<https://clinicaltrials.gov/ct2/show/NCT02420756>.

¹⁷ CMS.gov. Amyloid PET. September 27, 2013. <https://www.cms.gov/Medicare/Coverage/Coverage-with-Evidence-Development/Amyloid-PET>.

¹⁸ Global Alzheimer’s Platform Foundation. Global Alzheimer’s Platform Foundation® Applauds Neurologists for Speaking Out Against Proposed CMS Plan to Restrict Coverage to Alzheimer’s Patients. February 2, 2022.

<https://globalalzplatform.org/2022/02/02/global-alzheimers-platform-foundation-applauds-neurologists-for-speaking-out-against-proposed-cms-plan-to-restrict-coverage-to-alzheimers-patients/>.

¹⁹ Compare CMS, *Guidance for the Public, Industry, and CMS Staff: Coverage with Evidence Development* (Nov. 20, 2014), available at <https://www.cms.gov/medicare-coverage-database/view/medicare-coverage-document.aspx?MCDId=27> [hereinafter 2014 CMS CED Guidance] (noting that one principle governing the application of CED is to “generally expand access to medical technologies for beneficiaries”).

²⁰ ClinicalTrials.gov. Imaging Dementia-Evidence for Amyloid Scanning (IDEAS) Study. April 20, 2015.

<https://clinicaltrials.gov/ct2/show/NCT02420756>.

²¹ ClinicalTrials.gov. NEW IDEAS: Imaging Dementia-Evidence for Amyloid Scanning Study. June 11, 2020.

<https://clinicaltrials.gov/ct2/show/NCT04426539>.

The proposed CED also effectively limits enrollment in the clinical trials to relatively healthy beneficiaries without disqualifying comorbidities. As such, the proposed CED would exclude many beneficiaries who would not meet the CED-compliant RCT criteria. Unfortunately, the draft coverage decision doesn't explain how it would assure sufficient or equitable enrollment in the required trials given these limitations.

4. Delays in providing Medicare beneficiaries access to FDA-approved treatments for Alzheimer's disease may cause serious and irreparable harm.

The draft decision does not consider the burden and harm of its proposed policy – including the effective denial of treatment to all but a few thousand Alzheimer's disease patients for an unlimited period of time — and is therefore arbitrary and capricious.²²

CMS' draft acknowledges that the delay in providing treatment more broadly to Medicare beneficiaries may cause serious and irreparable harm. The proposal states that “anti-amyloid experts believe that interventions in later stages of disease (moderate to severe dementia especially) are too late: at that point amyloid has already triggered downstream processes such as pathologic tau accumulation, inflammation, and neurodegeneration. Once triggered, these downstream processes likely cannot be reversed by clearing amyloid.” CMS never reconciles its proposed policy with the inevitable delays and limitations it imposes on patients. The proposal inequitably limits access to a small portion of the Medicare patients who could benefit from the therapy and can access an enrolled research site. Meanwhile the progression of disease, for nearly all beneficiaries, would continue unabated.

C. The proposed NCD mischaracterizes existing evidence on amyloid-directed mAbs, and ADUHELM specifically, in a manner that is inconsistent with FDA's findings and contemporary scientific understanding.

For the reasons set forth below, the draft decision incorrectly concludes that the available evidence is insufficient to establish that using amyloid-directed mAbs to treat Alzheimer's disease is reasonable and necessary.²³ “An agency is required to ‘examine the relevant data and articulate a satisfactory explanation for its action

²² See, e.g., *Motor Vehicle Mfrs. Ass'n of U.S., Inc. v. State Farm Mut. Auto. Ins. Co.*, 463 U.S. 29, 43 (1983) (arbitrary and capricious where agency “entirely fail[s] to consider an important aspect of the problem”).

²³ Decision Memorandum.

including a rational connection between the facts found and the choice made.”²⁴ The failure to do so is arbitrary and capricious.²⁵

1. Reducing amyloid plaques is reasonably likely to predict clinical benefit.

The etiology of Alzheimer’s disease is not unknown. Alzheimer’s disease is an irreversible, progressive disease characterized by aggregation and deposition of amyloid and tau proteins and leading to degeneration and loss of neurons in the brain. And, FDA has made the determination that clearing amyloid is reasonably likely to result in clinical benefit.²⁶ FDA stated in its approval memorandum that “amyloid plaque is an underlying, fundamental, and defining pathophysiological feature of [AD].”²⁷ Further, it acknowledged that “[a]lthough the role of amyloid and its relationship to other pathophysiological features of Alzheimer’s disease, such as tau and neurodegeneration, is complicated, the presence of amyloid plaques is a primary and essential finding in Alzheimer’s disease, including early in the disease.”²⁸

Rare dominantly-inherited forms of Alzheimer’s disease, are caused by mutations in genes (APP, PSEN 1 and 2 genes) necessary for the production of amyloid beta (A β).²⁹ ApoE e4 genotype, the single biggest risk for sporadic Alzheimer’s disease, is implicated in clearance of A β from the brain.³⁰ Moreover, there is abundant published evidence confirming direct neurotoxic effects of aggregated A β , namely oligomers and plaques, and that A β toxicity triggers tau pathology and neurodegeneration.^{31,32,33}

Longitudinal PET imaging studies have consistently shown amyloid deposition preceding tau aggregation by several years^{34,35} and suggest A β amplifies the spread of

²⁴ *Dist. Hosp. Partners, L.P. v. Burwell*, 786 F.3d 46, 56–57 (D.C. Cir. 2015) (quoting *State Farm*, 463 U.S. at 43). The failure to do so is arbitrary and capricious.

²⁵ *Id.*

²⁶ ADUHELM [Prescribing Information]. Cambridge, MA: Biogen, June 2021.

²⁷ FDA Office of Neurology’s Summary Review Memorandum at 8.

²⁸ *Id.*

²⁹ Selkoe DJ, et al. The amyloid hypothesis of Alzheimer’s disease at 25 years. *EMBO Mol Med*. 2016 Jun 1;8(6):595-608. doi: 10.15252/emmm.201606210.

³⁰ Kim J, et al. The Role of Apolipoprotein E In Alzheimer’s Disease. *Neuron*. 2009 Aug 13;63(3):287-303. doi: 10.1016/j.neuron.2009.06.026.

³¹ Koffie RM, et al. Oligomeric amyloid beta associates with postsynaptic densities and correlates with excitatory synapse loss near senile plaques. *Proc Natl Acad Sci U S A* 2009 Mar 10;106(10):4012-7. doi: 10.1073/pnas.0811698106.

³² Kuchibhotl KV, et al. A β plaques lead to aberrant regulation of calcium homeostasis in vivo resulting in structural and functional disruption of neuronal networks. *Neuron*. 2008 Jul 31;59(2):214-25. doi: 10.1016/j.neuron.2008.06.008.

³³ Meyer-Luehmann M, et al. Rapid appearance and local toxicity of amyloid- β plaques in a mouse model of Alzheimer’s disease *Nature*. 2008 Feb 7;451(7179):720-4. doi: 10.1038/nature06616.

³⁴ Hansson O. Biomarkers for neurodegenerative diseases. *Nat Med*. 2021 Jun;27(6):954-963. doi: 10.1038/s41591-021-01382-x

³⁵ Dore V, et al. Relationship between amyloid and tau levels and its impact on tau spreading. *Eur J Nucl Med Mol Imaging*. 2021 Jul;48(7):2225-2232. doi: 10.1007/s00259-021-05191-9.

tau pathology.^{36,37} As FDA notes “mutations causing abnormalities in amyloid that result in autosomal dominant Alzheimer’s disease further reinforce [Aβ’s] fundamental role.”³⁸

Upon concluding that Aβ plaques have a role in Alzheimer’s disease, FDA found that there was “a strong group-level relationship” between the change from baseline in Aβ plaque standardized uptake value ratio (SUVR) and change from baseline in the Clinical Dementia Rating Sum of the Boxes (CDR-SB) clinical endpoint, establishing a “clear relationship between reduction of Aβ plaque burden in brain and preservation of clinical function in the aducanumab program.”³⁹ Therefore, it is “reasonable to conclude that treatment that is targeted at reducing amyloid plaque, and that successfully accomplishes that reduction, has the potential to convey clinical benefit.”⁴⁰

A recent meta-analysis by NIH scientists of seventeen Phase 3 trials on amyloid-directed mAbs concluded reduction in amyloid burden, as measured by amyloid PET scan, is correlated with cognitive outcomes.⁴¹ Further, the emergence and spread of tau pathology throughout the cortex closely correlates with cognitive decline and disease progression. In both the EMERGE (Study 302) and ENGAGE (Study 301) studies, ADUHELM treatment demonstrated reduction of amyloid plaques,⁴² as well as reduction in plasma p-tau.⁴³ Importantly, reduction of plasma p-tau correlated with slower clinical decline on the primary and all secondary clinical outcome measures in both EMERGE and ENGAGE.²⁷ Similar findings were observed among other second generation amyloid-directed mAbs, as discussed below.^{44,45} Thus, it is reasonably likely that the newer amyloid-directed mAbs may provide clinical benefit given that the new amyloid-directed mAbs reduce tau pathophysiology, and that tau pathophysiology more closely correlates with disease progression as measured by

³⁶ He Z, et al. Amyloid-β plaques enhance Alzheimer’s brain tau-seeded pathologies by facilitating neuritic plaque tau aggregation. *Nat Med.* 2018 Jan;24(1):29-38. doi: 10.1038/nm.4443.

³⁷ Long JM, et al. Alzheimer Disease: An Update on Pathobiology and Treatment Strategies. *Cell.* 2019 Oct 3;179(2):312-339. doi: 10.1016/j.cell.2019.09.001.

³⁸ Center for Drug Evaluation & Research. Drug Approval Package: ADUHELM (aducanumab-avwa): Office of Neurology’s Summary Review Memorandum. Food and Drug Administration. Page 8. June 7, 2021. Accessible at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2021/Aducanumab_BLA761178_Dunn_2021_06_07.pdf

³⁹ *Id.*

⁴⁰ *Id.*

⁴¹ Avgerinos KI, et al. Effects of monoclonal antibodies against amyloid-β on clinical and biomarker outcomes and adverse event risks: A systematic review and meta-analysis of phase III RCTs in Alzheimer’s disease. *Ageing Res Rev.* 2021 Jul;68:101339. doi: 10.1016/j.arr.2021.101339.

⁴² Budd Haeberlein S, et al. Evaluation of aducanumab efficacy in early Alzheimer’s disease [Presentation]. Alzheimer’s Disease and Parkinson’s Disease (AD/PD). March 9-14, 2021. Virtual.

⁴³ Hansson O, et al. Dose- and time- dependent changes in plasma p-tau181 in patients treated with aducanumab in the ENGAGE and EMERGE trials [Presentation]. Clinical Trials on Alzheimer’s Disease (CTAD). November 9-12. 2021. Boston, MA.

⁴⁴ Swanson CJ, et al. Lecanemab: An Assessment of the Clinical Effects, the Correlation of Plasma Aβ42/40 Ratio with Changes in Brain Amyloid PET SUVR, and Safety from the Core and Open Label Extension of the Phase 2 Proof-of-Concept Study, BAN2401-G000-201, in Subjects with Early Alzheimer’s Disease [Presentation]. Clinical Trials on Alzheimer’s Disease (CTAD). November 9-12. 2021. Boston, MA.

⁴⁵ Mintun MA, et al. TRAILBLAZER-ALZ study: Amyloid clearance results in a rapid and sustained reduction in plasma P-tau217 levels [Presentation]. Alzheimer’s Association International Conference (AAIC). July 26-30, 2021. Denver, CO.

sensitive, validated biomarker tests. A greater treatment effect on brain A β plaque levels is associated with greater treatment effects on clinical outcomes and on downstream markers of tau pathology.^{46,47,48,49} Accordingly, Biogen believes in the importance of confirming Alzheimer's disease pathology as part of diagnosis and supports Medicare coverage of diagnostic tools to do so.

2. *The proposed coverage decision inappropriately combines evidence for first- and second-generation amyloid-directed mAbs with more recent amyloid-directed mAbs.*

Unlike first generation amyloid-directed mAbs, ADUHELM and other second-generation amyloid-directed mAbs target aggregated forms of A β . FDA senior officials have distinguished ADUHELM from previous failed amyloid-directed mAbs in terms of Mechanism of Action. They have explained that drugs targeting A β in the past had little or no effect on A β plaques.⁵⁰ By contrast, more recent monoclonal antibodies, such as ADUHELM, donanemab, and lecanemab, reduce A β plaques significantly, and clinical trials in patients with Alzheimer's disease have demonstrated a relationship between the size of reduction of A β plaques and effect on clinical endpoints. In addition, past clinical studies used lower doses, targeted different epitopes, included clinical trial participants who did not have brain amyloid pathology or at later stages of Alzheimer's disease with a greater degree of irreversible neurodegeneration, or some combination thereof.

Newer, second generation amyloid-directed mAbs, like ADUHELM, implemented important learnings from the first generation amyloid-directed mAbs in their study designs, namely inclusion of participants in the early stages of Alzheimer's disease with confirmed amyloid pathology, the establishment of biomarker endpoints, and the investigation of higher doses.⁵¹ Second generation amyloid-directed mAbs selectively target aggregated A β and have demonstrated comparable results in amyloid plaque removal, reduction of tau biomarkers, and clinical

⁴⁶ Swanson CJ, et al. Lecanemab: An Assessment of the Clinical Effects, the Correlation of Plasma A β 42/40 Ratio with Changes in Brain Amyloid PET SUVR, and Safety from the Core and Open Label Extension of the Phase 2 Proof-of-Concept Study, BAN2401-G000-201, in Subjects with Early Alzheimer's Disease [Presentation]. Clinical Trials on Alzheimer's Disease (CTAD). November 9-12, 2021. Boston, MA.

⁴⁷ Mintun MA, et al. TRAILBLAZER-ALZ study: Amyloid clearance results in a rapid and sustained reduction in plasma P-tau217 levels [Presentation]. Alzheimer's Association International Conference (AAIC). July 26-30, 2021. Denver, CO.

⁴⁸ Rajagovindan R, et al. Reductions in Biomarkers of Alzheimer's Disease Pathophysiology Following Treatment with Aducanumab Were Associated with Slowing in Clinical Decline [Poster]. Alzheimer's Association International Conference (AAIC). July 26-30, 2021. Denver, CO.

⁴⁹ Hansson O, et al. Dose- and time-dependent changes in plasma p-tau181 in patients treated with aducanumab in the ENGAGE and EMERGE trials [Oral Presentation]. Clinical Trials on Alzheimer's Disease (CTAD). November 9-12, 2021. Boston, MA.

⁵⁰ Dunn B, et al. An Appropriate Use of Accelerated Approval - Aducanumab for Alzheimer's Disease. *N Engl J Med*. 2021 Aug 26;385(9):856-857. doi: 10.1056/NEJMc2111960.

⁵¹ van Dyck CH, et al. Anti-Amyloid- β Monoclonal Antibodies for Alzheimer's Disease: Pitfalls and Promise. *Biol Psychiatry*. 2018 Feb 15;83(4):311-319. doi: 10.1016/j.biopsych.2017.08.010.

outcomes.^{52,53,54,55} The proposed decision mentions in passing that there are key differences between the first and second generation of products but proceeds to include masses of trial data from first generation products like solanezumab and bapineuzumab while not mentioning supportive data from second-generation amyloid-directed mAbs like lecanemab and donanemab – data that was key to FDA’s assessment that clearing amyloid is reasonably likely to predict clinical benefit.

3. Clinical trial results demonstrate clinically meaningful therapeutic benefit of ADUHELM.

Biogen disagrees with the statement in the proposed NCD that no trial has been able to demonstrate a clinically meaningful improvement in patient health outcomes. FDA concluded that the EMERGE study “demonstrated a clinically meaningful and statistically significant treatment effect for the high dose of aducanumab on an accepted primary endpoint, the [Clinical Dementia Rating Sum of the Boxes scale (CDR-SB)], and across multiple secondary and tertiary endpoints.”⁵⁶ CMS’ proposal does not offer a reasoned explanation for disagreement with FDA’s determination regarding the clinical benefit of ADUHELM.

FDA’s Clinical, Statistical, and Safety reviews all supported Biogen’s protocol design, which provided strong evidence of both effect on brain amyloid plaque and improved attendant clinical outcomes.⁵⁷ The primary outcome measure in both EMERGE and ENGAGE was the Clinical Dementia Rating Sum of the Boxes scale (CDR-SB), a commonly used metric in Alzheimer’s disease clinical research. The CDR-SB is a scale that meaningfully assesses both cognitive and daily function in an integrated manner and is consistent with FDA guidance on appropriate endpoints for patients with early-stage Alzheimer’s disease. The FDA accepts statistically significant changes on an inherently meaningful instrument such as the CDR-SB as evidence of clinically meaningful effect.”⁵⁸ In agreement with the FDA, and external Alzheimer’s disease experts, the ADUHELM studies were designed to detect a 25% treatment effect.

⁵² Sevigny J, et al. The antibody aducanumab reduces A β plaques in Alzheimer's disease. *Nature*. 2016 Sep 1;537(7618):50-6. doi: 10.1038/nature19323.

⁵³ Arndt JW, et al. Structural and kinetic basis for the selectivity of aducanumab for aggregated forms of amyloid- β . *Sci Rep*. 2018 Apr 23;8(1):6412. doi: 10.1038/s41598-018-24501-0.

⁵⁴ Mintun MA, et al. Donanemab in Early Alzheimer's Disease. *N Engl J Med*. 2021 May 6;384(18):1691-1704. doi: 10.1056/NEJMoa2100708.

⁵⁵ Swanson CJ, et al. A randomized, double-blind, phase 2b proof-of-concept clinical trial in early Alzheimer's disease with lecanemab, an anti-A β protofibril antibody. *Alzheimers Res Ther*. 2021 Apr 17;13(1):80. doi: 10.1186/s13195-021-00813-8.

⁵⁶ Center for Drug Evaluation & Research. Drug Approval Package: ADUHELM (aducanumab-avwa): Office of Neurology’s Summary Review Memorandum. Food and Drug Administration. Page 41-42. June 7, 2021. Accessible at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2021/Aducanumab_BLA761178_Dunn_2021_06_07.pdf.

⁵⁷ Center for Drug Evaluation & Research. Drug Approval Package: ADUHELM (aducanumab-avwa). Clinical Review. Food and Drug Administration. Page 11-14. June 7, 2021. Accessible at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2021/761178Orig1s000MedR_Redacted.pdf.

⁵⁸ Food and Drug Administration. Combined FDA and Applicant PCNS Drugs Advisory Committee Briefing Document. Page 34. November 6, 2020. Accessible at: https://fda.report/media/143503/PCNS-20201106-CombinedFDABiogenBackgrounder_0.pdf

Secondary clinical outcome measures included the Mini-Mental State Exam (MMSE), a global cognitive evaluation measure used in research and in clinical practice, the Alzheimer’s disease Assessment Scale Cognitive 13 item subscale (ADAS-Cog 13), and the Alzheimer’s Disease research Cooperative Activities of Daily Living Inventory specific to MCI (ADCS-ADL-MCI) scale, which captures functional impairment in early-stage disease. These tools measure things that have a direct impact on patient’s ability to maintain independence, e.g., make phone calls, manage their financial affairs, self-care, etc. Notably, EMERGE demonstrated a 40% slower decline in function compared to placebo as measured by the ADCS-ADL-MCI scale after 78 weeks of treatment. The ENGAGE study was a negative study, but data are concordant between ENGAGE and EMERGE with the right dose and exposure. The Alzheimer’s Disease Patient and Caregiver Engagement (AD PACE) What Matters Most (WMM) study identified 42 clinical concepts most important to patients and caregivers. The primary and secondary scales used in the ADUHELM studies matched 25 out of 42 WMM concepts. When including the Neuropsychiatric Inventory (NPI) scale, there were 31/42 matches.⁵⁹

4. All the primary, secondary and tertiary clinical endpoints in EMERGE favored treatment over placebo, per the pre-specified statistical analysis plan.

As stated in the FDA review, the probability of reaching statistical significance by chance (type I error) on the primary and three secondary endpoints observed in EMERGE, is less than 1 in 10 million.⁶⁰

The proposed NCD inaccurately describes the analysis of EMERGE results as “post-hoc” and “secondary.” The primary analysis was not post hoc – it was prespecified per the Statistical Analysis Plan. Additional exploratory and sensitivity analyses then provided further support and were based on scientific rationale and under the guidance of a regulatory agency. The FDA states, “The purpose of these analyses is to provide maximum understanding of the partially discordant results and to determine if this understanding precludes independent consideration of Study 302.”⁶¹ Moreover, the data were collected before the decision to declare futility, not after the trials were stopped. The data characterized as “additional” were collected while the studies continued as planned, under double-blind conditions in accordance with existing protocols, until discontinuation of the studies was announced in March 2019. Contrary to the characterization in the proposed NCD, unblinding was never

⁵⁹ Hartry A, et al. The Importance of Care Partner Input in Alzheimer’s Disease (AD) Drug Development [Poster]. Alzheimer’s Association International Conference (AAIC). July 27-31, 2020. Virtual.

⁶⁰ Center for Drug Evaluation & Research. Drug Approval Package: ADUHELM (aducanumab-avwa). Clinical Review. Food and Drug Administration. Page 112. June 7, 2021. Accessible at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2021/761178Orig1s000MedR_Redacted.pdf.

⁶¹ Food and Drug Administration. Combined FDA and Applicant PCNS Drugs Advisory Committee Briefing Document. Page 64. November 6, 2020. Accessible at: https://fda.report/media/143503/PCNS-20201106-CombinedFDABiogenBackgrounder_0.pdf.

carried out for the purpose of data analysis.⁶² Post-hoc analyses demonstrated that both EMERGE and ENGAGE were concordant on the CDR-SB for participants who had 8 or more uninterrupted doses of 10 mg/kg and patients who achieved a minimum 150 mg/kg cumulative dosing over 78 weeks.⁶³

The proposal's analysis of the divergence between EMERGE and ENGAGE is likewise inaccurate. The proposal suggests an alternative explanation for the divergent results in the studies, namely differences in the placebo groups. This possibility was thoroughly tested and ruled out by FDA.⁶⁴ Demographic and clinical characteristics were balanced across all placebo and treatment arms in both studies, which limits the potential for differential placebo response. The placebo declines of the Phase 3 studies were in line with pre-specified expectation, and no systematic trend in placebo decline over time or across endpoints was observed.

The current draft proposal fails to consider FDA's analysis and introduces flawed thresholds for determining clinical benefit. The draft NCD invokes minimal clinically important difference (MCID), as estimated in Andrews et al, 2019, as the relevant standard for determining clinical benefit in clinical trials. The estimates of MCID by Andrews et al are based on a non-representative sample of patients from the National Alzheimer's Coordinating Center Uniform Data Set. These subjects did not have biological confirmation of Alzheimer's disease nor were they enrolled in clinical trials. The authors themselves acknowledged the limitations of MCID estimates, cautioning that "the present findings may represent conservative estimates, given that an unknown proportion of the sample deemed to have meaningful decline may have achieved a clinically important decline at a precise date before the annual follow-up assessment, thereby surpassing the MCID between visit periods. In other words, the MCID estimates from the present study may reflect change thresholds that are higher than the true MCID."⁶⁵ Amyloid-directed mAbs modify disease pathophysiology, unlike symptomatic medications. The 40% reduction on ADLs as shown in EMERGE, underscores that alteration of disease pathophysiology may grow overtime and can be measured in longer term RWE efforts. As part of Biogen's longstanding commitment to data generation for any therapy, ongoing studies including EMBARK and ICARE AD, as well as the forthcoming ENVISION study and the

⁶² The studies were eventually unblinded for certain analyses. As noted in FDA's clinical inspection summary: "An Authorization to Release Treatment Assignments for Protocol 221AD302 was signed on 3/21/2019 due to an 'urgent need for internal analysis upon the readout of the futility analysis'. Treatment assignment information was released to the Biogen Study Management Team (SMT) statistician. The sponsor released treatment assignments to the IQVIA statistics team on 4/18/2019 (as stated in the Statistical Analysis Plan [SAP] amendment dated 11/4/2019)."

⁶³ Krudys 2021, FDA Medical Review, p124 Table 39, p125-126 Figs 22,23,24,25.

⁶⁴ Center for Drug Evaluation & Research. Drug Approval Package: ADUHELM (aducanumab-avwa). Clinical Review. Food and Drug Administration. Page 112. June 7, 2021. Accessible at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2021/761178Orig1s000MedR_Redacted.pdf.

⁶⁵ 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 Aug 2;5:354-363. doi: 10.1016/j.trci.2019.06.005.

Clinical Data Research Network (CDRN, described below), will address all the questions posed by this draft proposal.

5. The proposed decision memorandum incorrectly interprets ADUHELM's safety profile, missing FDA's detailed analysis.

In granting accelerated approval, FDA's safety reviewers concluded that "[t]here are no safety issues that would preclude approval of aducanumab for the proposed indication."⁶⁶ As they noted, ADUHELM was "well-characterized in a safety database of adequate size." At the time of FDA's evaluation, more than 3,000 patients had been treated with aducanumab, over 2,000 person-years were exposed to the dosage ultimately approved (10 mg/kg), and more than 300 patients had received the approved dosage for more than 18 months.⁶⁷ The size of the database exceeded internationally agreed upon criteria for drugs intended for long-term use.⁶⁸

From this large body of data, FDA concluded that amyloid-related imaging abnormalities (ARIA), which are a known effect of amyloid-directed mAbs and are typically characterized by edema or small areas of bleeding, is the most important safety concern for treatment with ADUHELM.^{69,70} Yet symptomatic cases of ARIA were uncommon, and serious symptomatic cases even rarer. Only 24% of those who received the ultimately approved dose who then developed ARIA-experienced clinical symptoms. Serious symptoms associated with ARIA do occur but are rare (0.3% of patients in studies).^{71,72} The vast majority of ARIA cases were only detected radiographically—when patients underwent MRI scans at prespecified times during the studies. Moreover, the vast majority of ARIA cases resolved on their own within

⁶⁶ Center for Drug Evaluation & Research. Drug Approval Package: ADUHELM (aducanumab-avwa): Office of Neurology's Summary Review Memorandum. Food and Drug Administration. Page 11, 64. June 7, 2021. Accessible at:

https://www.accessdata.fda.gov/drugsatfda_docs/nda/2021/Aducanumab_BLA761178_Dunn_2021_06_07.pdf.

⁶⁷ Center for Drug Evaluation & Research. Drug Approval Package: ADUHELM (aducanumab-avwa): Office of Neurology's Summary Review Memorandum. Food and Drug Administration. Page 57. June 7, 2021. Accessible at:

https://www.accessdata.fda.gov/drugsatfda_docs/nda/2021/Aducanumab_BLA761178_Dunn_2021_06_07.pdf.

⁶⁸ Center for Drug Evaluation & Research. Office of Neuroscience's Clinical Review Memorandum — ADUHELM. Pages 28-29. June 6, 2021. Accessible at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2021/761178Orig1s000MedR_Redacted.pdf.

⁶⁹ Sperling RA, et al. Amyloid-related imaging abnormalities in amyloid-modifying therapeutic trials: recommendations from the Alzheimer's Association Research Roundtable Workgroup. *Alzheimer's Dement*. 2011 Jul;7(4):367-85.

⁷⁰ Center for Drug Evaluation & Research. Drug Approval Package: ADUHELM (aducanumab-avwa): Office of Neurology's Summary Review Memorandum. Food and Drug Administration. Page 11. June 7, 2021. Accessible at:

https://www.accessdata.fda.gov/drugsatfda_docs/nda/2021/Aducanumab_BLA761178_Dunn_2021_06_07.pdf.

⁷¹ Center for Drug Evaluation & Research. Drug Approval Package: ADUHELM (aducanumab-avwa): Office of Neurology's Summary Review Memorandum. Food and Drug Administration. Page 10, 61, 62. June 7, 2021. Accessible at:

https://www.accessdata.fda.gov/drugsatfda_docs/nda/2021/Aducanumab_BLA761178_Dunn_2021_06_07.pdf.

⁷² ADUHELM Prescribing Information. Pages 4-5. June 7, 2021. Accessible at:

https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/761178s000lbl.pdf.

12 to 16 weeks.⁷³ Perhaps most importantly, no deaths in studies 103, 301, and 302⁷⁴ were ultimately attributed to study treatment or the adverse effects of ARIA.⁷⁵

Following in-depth analysis of the data, FDA granted accelerated approval for ADUHELM without a Risk Evaluation and Mitigation Strategy (REMS), without any contraindications, and without a boxed warning.⁷⁶ Each of these measures are tools that FDA has to ensure the benefits of a drug outweigh the risks and/or address particular, heightened safety issues.⁷⁷ For ADUHELM, FDA conclusively determined that they were unnecessary based upon their evaluation of the data available to date.⁷⁸ Ongoing and continued safety monitoring from real-world use of ADUHELM is mandated by FDA policy, as it is for all FDA approved therapies, and may inform modification to the label as needed.

Additionally, Biogen performs ongoing pharmacovigilance to characterize the risk and monitoring for ARIA associated with the use of ADUHELM.⁷⁹ Biogen has a dedicated team of highly experienced healthcare professionals who perform enhanced pharmacovigilance for all reports of ARIA, including quarterly reports to FDA. Biogen has a very strong track record of transparency, scientific partnership, and advances in the field of safety, pharmacovigilance, and risk communication in the interest of patient safety.⁸⁰ Biogen will maximize the use of available data sources including from ENVISION, EMBARK, ICARE AD, post-marketing reports, published literature and real-world data analyses to ensure continued characterization and understanding of ARIA. Biogen is working with the experts and prescribers to advance our understanding of ARIA that helps inform our risk communication strategy. Biogen continues to work with the FDA and external experts to ensure that real-world prescribers are well-informed transparently on the diagnosis and management of ARIA.

⁷³ Salloway S, et al. Amyloid-Related Imaging Abnormalities in 2 Phase 3 Studies Evaluating Aducanumab in Patients with Early Alzheimer Disease. *JAMA Neurol.* 2022 Jan 1;79(1):13-21.

⁷⁴ Studies 103, 301, and 302 are the Phase 1b PRIME, Phase 3 ENGAGE, and Phase 3 EMERGE studies, which enrolled the vast majority of patients in the clinical program (more than 2900 of the patients who received at least one dose of aducanumab).

⁷⁵ FDA Division of Risk Management Review, Pages 11, 14; *accord* FDA Office of Neurology Summary, Pages 57-58. August 2019. Accessible at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2019/022075Orig1s000RiskR.pdf.

⁷⁶ ADUHELM [Prescribing Information]. Cambridge, MA: Biogen, June 2021.

⁷⁷ U.S. Food & Drug Admin., Guidance for Industry: Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products — Content and Format, Page 8. October 2011, Accessible at: <https://www.fda.gov/media/71866/download>; U.S. Food & Drug Admin., REMS: FDA's Application of Statutory Factors in Determining When a REMS is Necessary — Guidance for Industry, Pages 2-5. April 2019, Accessible at: <https://www.fda.gov/media/100307/download>.

⁷⁸ FDA Office of Neurology Summary, Page 64. June 7, 2021. Accessible at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2021/Aducanumab_BLA761178_Dunn_2021_06_07.pdf (REMS drug safety programs are typically established for products with concerning safety profiles).

⁷⁹ ADUHELM FDA approval letter. Page 5. June 7, 2021. Accessible at: https://www.accessdata.fda.gov/drugsatfda_docs/applletter/2021/761178Orig1s000ltr.pdf.

⁸⁰ Bloomgren, et al. Risk of Natalizumab-Associated Progressive Multifocal Leukoencephalopathy. *N Engl J Med* 2012; 366:1870-1880; Ryerson LZ et al. Risk of natalizumab-associated PML in patients with MS is reduced with extended interval dosing. *Neurology.* 2019 Oct 8;93(15):e1452-e1462.

The proposal doesn't capture this data or acknowledge the existing commitment to safety data collection and analysis and, in doing so, seemingly ignores FDA's findings regarding the safety of treatment with ADUHELM. In doing so, the proposed NCD artificially inflates the risks associated with ADUHELM treatment, to the detriment of patients.

D. The proposed NCD contradicts the clinical expertise of the FDA and sets an inappropriate precedent that would delay access to future therapies.

The misalignment between the FDA and CMS – both Department of Health and Human Services (HHS) agencies – regarding marketing authorization and Medicare coverage, respectively, for the same product is unprecedented. HHS publicly stated in its December 2021 update to the National Plan to Address Alzheimer's Disease that it would “prioritize and accelerate the pace of scientific research and ensure that as evidence-based solutions are identified, they are quickly translated, put into practice, and brought to scale so that individuals with AD/ADRD can benefit from increases in scientific knowledge.”⁸¹ Notwithstanding this statement, the agency's proposed NCD would *limit access* to the only therapy approved by the FDA in nearly 20 years based on a different analysis of the same data that the FDA reviewed.

Biogen believes CMS should align its coverage policy for Alzheimer's disease therapies with that of coverage policies for other therapies for progressive diseases, under which patients have immediate and equal access to medicines approved by the FDA for, at minimum, all approved indications.

Any additional restrictions due to ADUHELM's accelerated approval by FDA would be unwarranted and inappropriate. Congress expressly mandated the accelerated approval pathway, and FDA has implemented it for almost 40 years. As discussed above, the FDA's accelerated approval of ADUHELM was grounded in clinical data showing that ADUHELM impacted the underlying pathology of Alzheimer's disease, including a robust reduction in pathological hallmarks of Alzheimer's disease, specifically for both amyloid plaques and neurofibrillary tangles in the brain.⁸² FDA's accelerated approval is no less scientifically rigorous than other drug approvals through this statutory pathway, including many drugs for cancer and other serious diseases which CMS covers. All these diseases should be held to the same standards.

⁸¹Office of the Assistant Secretary for Planning and Evaluation. National Plan to Address Alzheimer's Disease. December 27, 2021. <https://aspe.hhs.gov/reports/national-plan-2021-update>.

⁸²ADUHELM [Prescribing Information]. Cambridge, MA: Biogen, June 2021.

1. *The proposal's application of CED to FDA-approved uses of a drug is inconsistent with the Medicare statute and CMS' rules and guidance.*

As a threshold matter, the proposed NCD does not apply the applicable statutory standards for evaluating whether a drug is “reasonable and necessary” for diagnosis, treatment, or to improve the functioning of a malformed body member.⁸³ Instead, the coverage analysis second-guesses the conclusive judgment of FDA as to whether ADUHELM is safe and effective, which is not CMS’ statutory role. FDA is the agency delegated with the authority under the Food, Drug, and Cosmetic Act (FDCA) to determine if a drug is “safe” and “effective.”⁸⁴ For these reasons, CMS must defer to FDA’s evaluation of safety and effectiveness; CMS’ role is to evaluate whether a safe and effective drug is “reasonable and necessary” when furnished to Medicare beneficiaries, considering the unique characteristics of this patient population.

The proposal as drafted does not offer a reasoned conclusion that amyloid-directed therapies are categorically not reasonable and necessary for their FDA-approved uses. Nor does the proposal offer any other principled basis for the conclusion that this class of FDA-approved therapies is categorically not reasonable and necessary. The proposed decision identifies nothing to suggest that there are special considerations that make amyloid-directed therapies—one of which FDA has determined to be safe and effective—clinically inappropriate for Medicare beneficiaries. And finally, the proposal does not identify unique characteristics of Medicare beneficiaries that make them unusually at-risk relative to the patient population evaluated by FDA.

The draft memorandum does not identify limitations in the clinical literature that suggest the Medicare population has not been adequately studied. The Alzheimer’s disease patient population is overwhelmingly comprised of Medicare-age beneficiaries, as was the population in the registrational clinical trials. As such, FDA has already conclusively evaluated clinical safety and efficacy in the Medicare beneficiary population. CMS must not transmute the statutory reasonable and necessary standard into second-guessing the considered judgment of FDA on issues of safety and efficacy. CMS has exceeded its authority under the Medicare statute,⁸⁵ and has departed from CMS’ own guidance.⁸⁶

⁸³ SSA § 1862(a)(1)(A).

⁸⁴ See, e.g., FDCA § 505; see, e.g., 86 Fed. Reg. 49,337 (Sept. 2, 2021); 35 Fed. Reg. 3,685 (Feb. 25, 1970).

⁸⁵ See e.g., *Util. Air Regulatory Grp. v. EPA*, 573 U.S. 302, 321–24 (2014) (agency action that exceeds statutory authority is invalid).

⁸⁶ See 2014 CMS CED Guidance (“CED will not duplicate or replace the FDA’s authority in assuring the safety, efficacy, and security of drugs, biological products, and devices.”).

2. The proposed decision also contradicts the Agency's own policies for evaluating whether a therapy is reasonable and necessary.

Under long-standing Medicare Program Integrity Manual guidance, CMS evaluates whether a therapy is reasonable and necessary by assessing whether it is: (1) safe and effective; (2) not experimental or investigational (except certain routine costs in clinical trials); and (3) appropriate, including the duration and frequency that is considered appropriate for the item of service, whether it is furnished in accordance with accepted standards of medical practice for diagnosis or treatment, and whether it meets certain other criteria.⁸⁷ CMS has not referenced these standards. Rather, CMS improperly applies a completely different and arbitrary standard, basing its evaluation on an assessment of “meaningful benefit.”

If CMS had applied standards outlined in the Medicare Program Integrity Manual guidance, the agency could not have concluded that amyloid-directed therapies are not reasonable and necessary for their FDA-approved uses. CMS has made abundantly clear that it defers to FDA on whether a drug is safe and effective, experimental or investigational, or generally accepted in the medical practice community. As CMS explains in guidance, “as a matter of national policy [...] drugs or biologicals approved for marketing by FDA are safe and effective when used for indications specified in their labeling. In addition, FDA-approved drugs also may be covered when used for indications other than those specified on their labeling as long as FDA has not specified such uses as non-approved. [...] Drugs that have not received FDA approval for marketing are considered experimental or investigational except for certain cancer drugs distributed by the National Cancer Institute (NCI).”⁸⁸ CMS has maintained this national policy through provisions in the Medicare Benefit Policy Manual on coverage of approved uses of drugs and unlabeled uses of drugs.⁸⁹

3. The proposed application of CED to approved uses of an FDA-approved drug is unprecedented and arbitrarily holds FDA-approved therapies for Alzheimer's disease to a higher standard than therapies in any other disease states.

The proposal's treatment of amyloid-directed therapies for Alzheimer's disease is arbitrary, capricious, and inconsistent with how CMS treats all other FDA approved drugs, including hundreds of other drugs approved under accelerated approval pathways. In recent history, the agency has implemented *only one* NCD for a drug or biological requiring CED and, notably, has never before applied CED to FDA-approved uses of approved drugs. The only CED policy for drugs is in the NCD for Anti-Cancer Chemotherapy for Colorectal Cancer, which applies CED limitations on

⁸⁷ Medicare Program Integrity Manual, ch. 13 § 13.5.4.

⁸⁸ 54 Fed. Reg. 4,384, 4,306 (Jan. 30, 1989).

⁸⁹ Medicare Benefit Policy Manual, ch. 15, §§ 50.4.1 and 50.4.2.

coverage of unapproved, or “off-label” uses of Oxaliplatin (ELOXATIN™), irinotecan (CAMPTOSAR®), cetuximab (ERBITUX™), and bevacizumab (AVASTIN™).⁹⁰ Further, these restrictions apply only to a subset of off-label uses that are not supported by one or more CMS-recognized medical compendia. There is no precedent for CMS imposing CED restrictions on a labeled indication of a drug that FDA has approved and deemed safe and effective.

To the contrary, CMS has consistently rejected the idea of imposing CED restrictions for a drug’s FDA approved uses. For example, in 2011, CMS issued the NCD for Autologous Cellular Immunotherapy Treatment of Metastatic Prostate Cancer—which specifically rejected use of CED restrictions for approved uses of the biologic PROVENGE®. The agency determined that the therapy was reasonable and necessary for its FDA-approved use.⁹¹ More recently, CMS also rejected CED restrictions for Chimeric Antigen Receptor T-Cell (CAR-T) therapies. CMS originally proposed CED for CAR-T therapies but reversed course in the agency’s final decision memo. CMS acknowledged that “CAR T-cell therapy is known to have a significant risk for toxicity, which is reflected in the FDA requirements for a REMS program and a boxed warning in the labeling”⁹² But the agency nonetheless rejected the need for CED in light of FDA’s prior evaluation of safety and effectiveness. CMS acknowledged that “[c]urrent FDA indications” necessarily reflect the “current clinical evidence” supporting use of CAR T-therapy.⁹³ CMS authorized coverage without CED in REMS approved facilities for “medically accepted indications”—including all FDA-approved indications and off-label uses supported by one or more CMS-approved compendia.⁹⁴

In its current proposal, CMS would hold FDA-approved therapies for Alzheimer’s disease to a different standard than it has previously applied to therapies in any other disease state, including other accelerated approval drugs. As a policy matter, this will improperly restrict beneficiary access to an entire class of Alzheimer’s disease treatments. And, as a legal matter, it is arbitrary and capricious: A fundamental rule of administrative law is that agencies must treat similarly situated entities the same.⁹⁵

⁹⁰ NCD for Anti-Cancer Chemotherapy for Colorectal Cancer, No. 110.17 (January 28, 2005).

⁹¹ See Decision Memo for Autologous Cellular Immunotherapy Treatment of Metastatic Prostate Cancer, CAG-00422N (June 30, 2011) (finding the therapy reasonable and necessary for treating patients with asymptomatic or minimally symptomatic metastatic castrate-resistant (hormone refractory) prostate cancer).

⁹² Decision Memo for CAR-T Therapy for Cancers, CAG-00451N (Aug. 7, 2019).

⁹³ *Id.*

⁹⁴ *Id.*

⁹⁵ *Melody Music, Inc. v. FCC*, 345 F.2d 730, 733 (D.C. Cir. 1965); see also *Cnty. of L.A. v. Shalala*, 192 F.3d 1005, 1022 (D.C. Cir. 1999); *FCC v. Fox Television Stations, Inc.*, 556 U.S. 502, 515 (2009) (agency must explain departures from past practice); *Lilliputian Sys., Inc. v. Pipeline & Hazardous Materials Safety Admin.*, 741 F.3d 1309, 1313 (D.C. Cir. 2014) (“As a general matter, an agency cannot treat similarly situated entities differently unless it ‘support[s] th[e] disparate treatment with a reasoned explanation and substantial evidence in the record.’”).

Biogen urges CMS to reverse its position and issue a final NCD that provides coverage for FDA-approved uses of amyloid-directed mAbs. In doing so, CMS would apply its long-standing and appropriate practice of deferring to the FDA on determinations of safety and efficacy, and facilitate beneficiary access to such treatments, consistent with CMS' statutory role under the Medicare Act and its own long-standing policies.⁹⁶

4. *The proposed RCT requirement risks undermining the FDA's Accelerated Approval Pathway.*

The draft NCD's proposed RCT requirement undermines the entire purpose of the FDA's accelerated approval pathway: to provide patients without other treatment options access to products based on surrogate endpoints. In effect, CMS is indefinitely limiting coverage for beneficiaries outside of small agency-approved RCTs after the FDA found ADUHELM to be safe and effective, and granted approval. Even if the required endpoints are met in CED-required RCTs, the proposed NCD provides no option for coverage outside of a study and no timeline for reconsidering the underlying evidence or assumptions upon which the NCD was based.

The Accelerated Approval Pathway is an important mechanism for approving effective therapies to address critical unmet patient needs in challenging and serious disease states. Drugs granted accelerated approval must meet the same rigorous standards of evidence for safety and effectiveness as those granted traditional approval, just against endpoints that can be evaluated more quickly to facilitate patient access. Once an accelerated approval drug is determined to be safe and effective by FDA, it is allowed to be marketed for its approved indications, even while a rigorous trial is conducted to confirm clinical benefit. Congress expressly designed this system with patients like those with Alzheimer's disease in mind. Those patients should not be denied access to treatment while the sufficiency of the surrogate endpoint is confirmed. Otherwise, the statutory provision for accelerated approval would be effectively read out of the law.

5. *The CED proposal would stifle innovation and set a precedent for coverage of FDA-approved indications of drugs.*

CMS' proposal, if finalized, would stifle innovation and set a harmful precedent for coverage of FDA-approved indications of drugs that address a significant unmet need. CMS' proposed restrictions on coverage would severely impact future investment and research into therapeutic options for patients with Alzheimer's disease. Its impact could also extend well beyond this class of medicines: CMS risks

⁹⁶ See 54 Fed. Reg. 4,384, 4,306 (Jan. 30, 1989), accord Medicare Benefit Policy Manual, ch. 15, §§ 50.4.1 and 50.4.2.

undermining the entire FDA accelerated approval pathway, instead of supporting access to therapies while confirmatory studies are conducted. This would have a chilling effect on access to promising new therapies—because developers of novel therapies need certainty that patients will be able to access these therapies upon FDA approval, given that each new treatment requires countless years and often billions of dollars in research and investment.

Biogen does not support CED restrictions that would curtail the ability to rely on FDA’s accelerated approval pathway to bring new therapies to patients. The accelerated approval pathway encourages scientific and medical advancement and innovation by leveraging the use of surrogate or intermediate clinical endpoints that are reasonably likely to predict clinical benefit. The approval of the first HIV/AIDS drug, based on the use of surrogate endpoints, prolonged and saved the lives of millions of patients who did not have any other therapeutic options.⁹⁷ Hence, this pathway provides hope that chronic conditions need not be a death sentence. If anything, the agency should adopt policies that encourage use of accelerated approval pathways—given the profound benefits earlier access to therapies has for beneficiaries with serious medical conditions for which there are currently no treatment options.

E. CED will impair equitable access to clinically appropriate Alzheimer’s disease care and exacerbate disparities in the diagnosis and treatment of Alzheimer’s disease.

The proposed policy would disproportionately harm Alzheimer’s disease patients compared to patients with other diseases, and disproportionately affect low-income individuals, dual-eligible beneficiaries, patients of color, veterans, and women. While we agree that “CMS should support evidence development for certain innovative technologies that are likely to show benefit for the Medicare population,”⁹⁸ and support CMS’s desire to see better diversity in clinical trials, we believe that CMS’ proposed decision will in practice have the opposite effect. Because Alzheimer’s disease disproportionately affects minorities, the proposed policy will similarly disproportionately affect this underserved population – and holds them to a different standard than CMS has repeatedly used for diseases that do not have such an epidemiological pattern.

Participation by a diverse sample of patients is a challenge in all trials across most diseases. It is a problem rooted in long-standing differences in access to care

⁹⁷ PhRMA. Accelerated Approval: Bringing patients access to needed medicines. October 6, 2021. <https://phrma.org/-/media/Project/PhRMA/PhRMA-Org/PhRMA-Org/PDF/A-C/Accelerated-approval--Bringing-patients-access-to-needed-medicines-2.pdf>.

⁹⁸ CMS, Guidance for the Public, Industry, and CMS Staff: Coverage with Evidence Development.

and historically well-founded suspicions about participating in clinical research. Academic medical centers and community hospitals that operate RCTs disproportionately enroll a high percentage of white patients compared to dedicated sites and private practices that enroll more diverse patients.⁹⁹ As such, the proposed requirement of an epidemiologically representative sample of the US population will do little to address health inequities and will instead exacerbate them.

In reality, the proposed requirements – including site-of-service limitations to hospital outpatient departments – will mean that there are only a handful of locations in the United States that will be able to support a CMS-approved CED trial—predominately academic medical centers or similar large health care systems. Many clinicians are not affiliated with large health care systems or aware of research efforts, even if nearby.¹⁰⁰ As a result, patients, based on geography alone, will be denied coverage for an FDA-approved drug to treat Alzheimer’s disease.

The site-of-service limitations also have significant ramifications that have not been addressed. Denying patients access to coverage based on geography poses serious equity concerns. Low-income and other underserved populations are the least likely to have the resources necessary to travel to academic centers. Furthermore, academic centers will prioritize established patients, making it difficult for new patients to receive treatment. And lastly, the NCD as proposed does not consider the patient harm associated with forcing patients to transition their care to a new provider. Most patients receive care in the community setting, and the CED would force such patients to receive a portion of their care outside the community rather than from doctors who know them well. The proposed CED policy, with its complex and limiting requirements, does nothing to improve equity in dementia detection, treatment, and management. In fact, it would almost certainly do the opposite. The mere fact of using a CED design (especially one as complex as an RCT) will leave out most members of underserved populations that have a higher incidence rate of Alzheimer’s disease.

As Biogen has previously commented, recognition and early detection of MCI and Alzheimer’s disease, and access to treatment and support services are especially lacking among Latinx American and Black/African American patients who are one-and-a-half to two times more likely to develop Alzheimer’s disease.¹⁰¹ These patients’ unmet needs include access to effective cognitive screening and relevant specialists, and public health education to address cultural biases and lack of knowledge

⁹⁹ Tufts Center for the Study of Drug Development. Impact Report Nov/Dec 2021. <https://f.hubspotusercontent10.net/hubfs/9468915/Impact%20Report%20Preview.png> (Minority groups express hesitancy towards interest in clinical trial enrollment. For example, 69% of Black Americans compared to 49% of White Americans cite they “don’t want to be a guinea pig” as a reason for not enrolling. Additionally, Native Americans lead all ethnic groups (36%) when they cite their doubt of clinical benefit as a reason to not enroll (Alzheimer’s Association 2020).

¹⁰⁰ Woodcock J, et al. Integrating Research into Community Practice- Toward Increased Diversity in Clinical Trials. *N Engl J Med.* 2021 Oct 7;385(15):1351-1353. doi: 10.1056/NEJMp2107331.

¹⁰¹ 2020 Alzheimer’s Disease Facts and Figures. Alzheimer’s Association. March 2020.

regarding normal aging and dementia. At the same time, inadequate health insurance coverage and racial biases among some health care providers and in the health care system can further lead to delay or missed opportunities for early detection, intervention, treatment, and support.

Underdiagnosis stems from several factors, including a misperception of AD-related symptoms as natural part of aging, barriers to access to qualified medical professionals, and a lack of information about Alzheimer’s disease and available services.^{102, 103} Underdiagnosis of Alzheimer’s disease can result in delayed treatment and management, worse outcomes, and increased downstream costs; those with undiagnosed dementia tend to have access to fewer health services than individuals with a formal diagnosis of dementia.¹⁰⁴

Biogen continues to be committed to finding ways to increase representation. For example, we have announced that both our real-world registry, ICARE AD, and our Phase 4 post-marketing confirmatory trial, ENVISION, intend to enroll 16%-18% of Black/African American and Latinx participants. However, we are deeply concerned that CMS’ proposed CED restrictions will compound the already pervasive inequities in access to treatment and will ultimately prove highly detrimental to health equity. Additionally, we are concerned about CMS’ arbitrary decision to restrict the usage of this class of therapies to the outpatient hospital setting. As noted in our previous comments,¹⁰⁵ we support appropriate oversight of treatment by qualified providers. However, this proposal would eliminate some of the top memory centers and neurology clinics in the country.

F. Any application of CED would duplicate investigative efforts, delay access to treatment, and create a significant burden on providers and patients.

CMS’ own guidance for use of CED mandates that CMS “not duplicate or replace the FDA’s authority,” not “unjustifiably duplicate existing knowledge,” and not use CED “when less restricted coverage is justified by the available evidence.” By mandating additional RCTs, the CED proposal violates each of these standards and thus runs afoul of the Administrative Procedure Act’s prohibition against arbitrary and capricious agency action.

¹⁰² Amjad, et al., Underdiagnosis of Dementia: An Observational Study of Patterns in Diagnosis and Awareness in US Older Adults. 2018; J Gen Intern Med 22(7): 1131-1138.

¹⁰³ HHS ASPE, Racial and Ethnic Disparities in Alzheimer’s Disease: A Literature Review, February 2014, available at [Racial and Ethnic Disparities in Alzheimer’s Disease: A Literature Review \(hhs.gov\)](https://www.aspe.hhs.gov/reports-and-publications/racial-and-ethnic-disparities-in-alzheimers-disease).

¹⁰⁴ Power et al., Racial disparities and temporal trends in dementia misdiagnosis risk in the United States. *Alzheimers Dement (N Y)*. 2019 Dec 9;5:891-898. doi: 10.1016/j.trci.2019.11.008.

¹⁰⁵ Biogen comments on NCA Tracking Sheet, August 11, 2022, <https://www.cms.gov/medicare-coverage-database/view/ncacal-public-comments.aspx?ncald=305&fromTracking=Y&>.

ADUHELM received accelerated approval by the FDA based on the detailed review of the results from RCTs, yet the proposed CED calls for additional RCTs to prove safety and clinically meaningful efficacy of treatment, which, as discussed, is duplicative with existing and ongoing efforts. Even without CED, ADUHELM, like all accelerated approval drugs, is subjected by the FDA to a confirmatory study requirement, which will adhere to FDA's well-established standards for appropriately designed RCTs for approval of individual therapeutic agents in the class. Given both the available evidence and the current pipeline of new evidence under development, the proposed CED requirement would either duplicate or undermine robust efficacy and safety data collection efforts already in place, inappropriately duplicate and replace FDA authority, and unnecessarily restrict coverage. As such, we strongly believe that CMS reverse course, rather than violate its own policies, which require deference to the FDA's scientific expertise to assess whether its criteria for safety and efficacy have been met, and where benefits outweigh risks.

The proposed requirement for an RCT is a direct duplication of FDA's requirement for a post-marketing confirmatory study. Biogen has already committed to multiple, rigorous clinical studies, already planned or underway, for ADUHELM that will provide evidence to address the same areas of inquiry raised by the proposed NCD. These include our Phase 4 confirmatory trial (ENVISION) and long-term follow-up study of participants in the original clinical trials (EMBARK). For ENVISION, Biogen anticipates submitting the final protocol for FDA review in March 2022, and initiation of patient screening in May 2022 with the primary completion date anticipated approximately four years later. The primary endpoint for ENVISION will be the Clinical Dementia Rating–Sum of Boxes (CDR–SB) at 18 months after ADUHELM treatment. This endpoint is consistent with the EMERGE and ENGAGE studies and will generate robust outcomes to verify the efficacy of treatment with ADUHELM. Meanwhile, the EMBARK study, an open-label long-term safety study of patients who had previously participated in the PRIME, EVOLVE, EMERGE, or ENGAGE clinical trials (1,696 participants), will examine the long-term safety and effectiveness of ADUHELM.¹⁰⁶

1. CMS has previously acknowledged that patient access and operational concerns undermine the feasibility of CED for drugs.

The agency cited patient access and operational concerns in not finalizing a proposed CED policy for other therapies.¹⁰⁷ Furthermore, CMS has also expressed

¹⁰⁶ ClinicalTrials.gov. A Study to Evaluate Safety and Tolerability of Aducanumab in Participants with Alzheimer's Disease Who Had Previously Participated in the Aducanumab Studies 221AD103, 221AD301, 221AD302 and 221AD205, January 27, 2020, <https://clinicaltrials.gov/ct2/show/NCT04241068>.

¹⁰⁷ CMS, Decision Memorandum for Erythropoiesis Stimulating Agents (ESAs) for non-renal disease indications (July 30, 2007) (ESAs for non-renal disease indications CED: "We have strongly considered, as many commenters suggested, whether this indication would be appropriate for CED. However, CED restricts coverage to within research studies. Coverage would not be available to any patients

concern regarding the agency's ability to manage CED studies, a concern that remains, in our view, relevant here.¹⁰⁸ This includes challenges the agency would face in initiating, managing, and executing a CED policy. If anything, these problems are compounded here by the unusually burdensome CED criteria that CMS has proposed. Biogen suggests the agency adopt an approach to coverage that better balances deference to the FDA on safety and efficacy, patient access, and continued data generation. Failure to do so would be arbitrary and inconsistent with its previous conclusions on this subject.¹⁰⁹

2. *The proposed CED requirements would impose a significant burden on patients, their caregivers, and providers, which could further limit patient access.*

Providers would also face significant operational challenges and administrative burdens under the proposed CED paradigm. To meet the requirements of CED, providers may need to train and hire new research coordinators, billing resources, and other staff. Furthermore, providers may also be required to obtain Institutional Review Board approvals and patient consent to undertake the proposed CED study, which may raise fundamental ethical concerns for patients and their care partners (i.e. randomization, cost-sharing for placebo) and create risks of coercion or undue influence on vulnerable patients.¹¹⁰ The additional provider administrative burden may detract from clinical priorities and dilute the quality of data, and uncertainty associated with CED has the potential to discourage providers from participating in CED, thus further limiting patient access. The U.S. health care system is already projected to have severe capacity constraints and delays to treatment for Alzheimer's disease patients.¹¹¹ Increasing administrative requirements for the limited number of providers will likely result in further prolonging wait times for treatment. The failure to consider these concerns is arbitrary and capricious.¹¹²

The prohibitive cost of managing RCTs, as proposed, can run into the hundreds of millions of dollars. The burden of such a requirement will likely discourage many potential study sponsors from pursuing the FDA's accelerated approval pathway for innovative Alzheimer's disease treatments. Additionally, due to the lack of coverage outside of a trial, this proposal would eliminate any possibility of Real-World Evidence (RWE) generation.

outside the study. We have considered options that would enroll beneficiaries initially into observational studies that could be used to assist in designing the appropriate randomized trial. However, the complexities of this option exceed the Agency's current ability to manage those vastly differing studies.").

¹⁰⁸ *Id.*

¹⁰⁹ *See, e.g., Cty. of L.A.*, 192 F.3d at 1022 (agency cannot treat similar situations differently without adequate explanation).

¹¹⁰ 42 C.F.R. § 42.111(a)(3); *see also* 45 CFR 46.111(a)(3).

¹¹¹ Liu, et al. Assessing the preparedness of the U.S. health care system infrastructure for an Alzheimer's Treatment. https://www.rand.org/pubs/research_reports/RR2272.html.

¹¹² *See State Farm*, 463 U.S. at 43.

Conclusion

As a pioneer in neuroscience, Biogen is committed to the ongoing development of real-world evidence to inform the value of ADUHELM. Biogen has repeatedly spearheaded evidence generation in the therapeutic areas we have pioneered, including multiple sclerosis and spinal muscular atrophy. **We are again committed to evidence generation for ADUHELM through RWE efforts such as ICARE AD, CDRNs, and Medicare claims analyses and will make these data readily available to CMS, FDA, NIH, and the broader scientific community. This RWE generation, however, will only be possible if CMS provides coverage for FDA-approved agents in the class. Therefore, we disagree with CMS' proposal to apply CED to ADUHELM and the entire class of amyloid-directed mAbs.**

We continue to invest in clinical development activities to bring new, safe, and more effective treatments for Alzheimer's disease to patients. However, the lack of appropriate coverage for ADUHELM and future class entrants for Medicare beneficiaries living with MCI due to Alzheimer's disease and mild Alzheimer's disease is in direct conflict with the recommendation of Alzheimer's disease experts.¹¹³ The proposed NCD would inappropriately restrict access for patients living with Alzheimer's disease, exacerbate health inequities, burden providers, and unnecessarily duplicate or undermine evidence-generation activities that are already ongoing.

The Alzheimer's community has waited years for advances in therapies. Confining coverage to beneficiaries enrolled in RCTs will effectively deny access for the vast majority of patients with Alzheimer's Disease to the first FDA-approved treatment for Alzheimer's disease in 20 years and, as explained above, will not support generation of new data beyond existing efforts. Narrow and complex coverage requirements that do not take into consideration a rapidly evolving clinical landscape could have the potential to stifle innovation and inappropriately limit access for beneficiaries living with Alzheimer's disease today and in the future.

Biogen, therefore, respectfully urges CMS to cover FDA-approved amyloid-directed mAbs for the treatment of Alzheimer's disease in accordance with their approved indications, consistent with the populations studied in their respective registrational clinical trials and guided by expert recommendations for appropriate clinical practice.¹¹⁴

¹¹³ Cummings J, et al. Aducanumab: Appropriate use recommendations. *Alzheimers Dement*. 2021 Jul 27;10.1002/alz.12444. doi: 10.1002/alz.12444.

¹¹⁴ Cummings J, et al. Public Policy Should Foster Alzheimer's Treatment Availability: Comment on the Draft US Medicare Decision to Limit Payment for Aducanumab (ADUHELM™) to Patients Participating in Clinical Trials. *J Prev Alz Dis*. Published online February 4, 2022, <http://dx.doi.org/10.14283/jpad.2022.25>.

We remain available to work with CMS and the Alzheimer's disease community to ensure that Medicare beneficiaries have timely and appropriate access to new innovative therapies to treat Alzheimer's disease.

* * *

We appreciate your consideration of this important matter. Please do not hesitate to contact me at priya.singhal@biogen.com if we can offer any additional information.

Sincerely,

A handwritten signature in black ink that reads "P. Singhal". The signature is written in a cursive style with a horizontal line underneath the name.

Priya Singhal
Head, Research and Development