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*BY ELECTRONIC DELIVERY* (CAGinquiries@cms.hhs.gov)

Tamara Syrek Jensen
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Centers for Medicare & Medicaid Services
7500 Security Boulevard
Baltimore, MD 21244

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

Dear Director Syrek Jensen:

Eli Lilly and Company (Lilly) appreciates the opportunity to comment on the proposed coverage decision for Monoclonal Antibodies Directed Against Amyloid for the Treatment of Alzheimer's Disease (Proposed NCD).[1] Lilly has been committed to Alzheimer's research for more than 30 years and remains determined to find solutions for this unrelenting and fatal disease. Our company has advanced the science of Alzheimer's Diseases (AD) diagnosis and treatment by discovering and commercializing imaging agents that permit the visualization of amyloid plaques and tau tangles—pathological hallmarks of AD—in the living brain. With donanemab, our latest therapeutic to enter Phase III clinical development, Lilly believes we are on the brink of meaningful change for people living with Alzheimer's. However, the potential benefits of amyloid plaque-reducing therapies, including those approved in the future, can become reality only if patients have timely and equitable access to both therapies and diagnostics. We are concerned that the Proposed NCD will impede that access for several years and contribute to unnecessary suffering and irreversible decline for people living with AD and their caregivers.

Lilly is proud of the data that we have already published in the *New England Journal of Medicine* and excited for the data that are to come soon on donanemab, and we have a duty to advocate for fair patient access to this drug based on its clinical evidence. Patient access to one drug, especially in a disease state with such high unmet need, should not be limited due to the data, published or unpublished, of another. While the launch of another anti-amyloid therapy has generated significant public debate, we fear that the Proposed NCD is an overreaction that undermines the promise of an entire drug class in response to a single controversial approval and launch. **We therefore strongly urge the Centers for Medicare & Medicaid Services (CMS) to revise the Proposed NCD to provide automatic national coverage for on-label use of anti-amyloid treatments where confirmatory data demonstrate slowing of decline in cognition and function; alternatively, CMS should issue NCDs on a drug-by-drug basis.** We believe this is necessary because:

- The Proposed NCD undermines the clear intent of Congress and exceeds CMS' authority.
- The Proposed NCD should not treat all monoclonal antibodies directed against amyloid the same.
- The restrictive Coverage with Evidence Development (CED) requirements of the Proposed NCD raise serious practical, policy, and ethical concerns.

[1] CMS, National Coverage Analysis (NCA), Proposed Decision Memo: Monoclonal Antibodies Directed Against Amyloid for the Treatment of Alzheimer's Disease. (Published January 11, 2022). Available at https://www.cms.gov/medicare-coverage-database/view/ncacal-decision-memo.aspx?proposed=Y&NCAId=305

Revising the Proposed NCD to provide automatic coverage to label for drugs with replicated, demonstrable clinical benefit will help address the multiple shortcomings of this proposal. Any CED, if adopted, should only supplement full coverage by encouraging additional data development for new uses or patient populations—a research agenda to which Lilly is already strongly committed. Alternatively, issuing NCDs on a drug-by-drug basis is a logical and defensible approach. CMS's purported rationale for a class-wide decision is that anti-amyloid mAbs "have a similar function of reducing amyloid in the brain." This characterization is cursory and overly simplistic.

If finalized, the Proposed NCD will doubtlessly have a chilling effect on Alzheimer's research, both now and in the decades to come. Innovative manufacturers and research investors have choices as to where to invest their research dollars. If CMS makes AD research investment unattractive, entities will shift investment to oncology or other diseases where these types of barriers do not exist. Risks will be taken elsewhere and people with AD will continue to wait for a cure.

## I. The Proposed NCD Undermines the Clear Intent of Congress and Exceeds CMS's Authority.

Congress has spoken clearly: the Department of Health and Human Services (HHS) is to do everything in its power to find and deploy effective treatment options for Americans suffering with AD by 2025. This is clear not just from the National Alzheimer's Project Act (NAPA) but also from the various amendments to the Food, Drug and Cosmetic Act (FDCA) that support faster approval of drugs for serious conditions that fill an unmet medical need. But rather than give force to Congress' clear desire to spur innovation for drugs that show promise against devastating diseases with no known cure like AD, CMS has instead opted to affirmatively disfavor AD drugs and patients by proposing to implement the most restrictive form of coverage, an NCD with CED. The procedural impediments created by an NCD with CED are almost never applied to FDA approved therapeutics. In fact, CMS has never before finalized an NCD that denied national coverage for on-label use of a therapeutic deemed safe and effective for the Medicare population by FDA. Moreover, this concept is not found anywhere in statute or in any legally binding regulations promulgated by HHS. Nonetheless CMS proposes to apply it arbitrarily to products not yet evaluated by FDA.

### *A. The Proposed NCD is Inconsistent with Requirements of the National Alzheimer's Project Act and the National Plan to Address Alzheimer's Disease.*

Passed by unanimous consent in both chambers of Congress and signed into law by President Obama in 2011, the National Alzheimer's Project Act directed HHS to, among other things, create and maintain an *integrated* national plan to overcome AD, provide information and coordination of AD research and services across all Federal agencies, *accelerate the development* of treatments that would prevent, halt, or reverse the course of AD, and to *improve the early diagnosis* of AD and coordination of the care and treatment of citizens with AD.[2] The Proposed NCD runs directly contrary to those goals.[3]

The Proposed NCD fails to honor Congress' mandate in at least three critical ways:

[2] Pub. L. No. 111-375, § 2(c) (Jan. 4, 2011).

[3] At the January 24, 2022 meeting of the Advisory Council on Alzheimer's Research, Care, and Services, multiple patients, and at least two other organizations in addition to Eli Lilly raised concerns regarding the impact of the Proposed NCD on patient access to this novel class of medications as well as the ways in which the Proposed NCD may frustrate the goals of the NAPA and the National Plan.

- First, CMS's approach is not "integrated" or "coordinated" with the FDA or other parts of CMS. Specifically, CMS will only provide Medicare coverage if it "approves" a "randomized controlled trial" (RCT) for a monoclonal antibody that clears amyloid plaques from the brain. To satisfy CMS's requirements for trial "approval", manufacturers must satisfy more than 20 requirements pertaining to patient criteria, research questions, and study requirements. Unless CMS clarifies that its RCT requirements are coterminous with FDA approved registration trials, then these onerous, expensive, and time-consuming clinical trial requirements effectively render FDA's judgment meaningless. If HHS is required to coordinate its approach to AD then it should clearly not permit different agencies within the Department to impose separate or redundant clinical trial requirements. This is inefficient and wholly incompatible with the NAPA.

  Relatedly, the Coverage and Analysis Group's (CAG's) actions also appear to lack coordination and integration with the Office of Actuary (OACT) in CMS. CAG and OACT obviously did not coordinate with respect to the likely impact of FDA approved AD therapies on Part B premiums as OACT's premium estimates clearly rely on the presumption of broad access, not the CAG's proposed policy of virtually no access. This disconnect is evident from CMS's announced Medicare Part B premium rates for 2022, which established a $21.60 per month increase in the standard Part B premium, from $148.50 in 2021 to $170.10 in 2022.[4] This 14.5 percent hike in premiums amounts to the largest Part B premium increase in the history of the Medicare program.[5] CMS officials have indicated that about half of the Part B premium increase for 2022 is due to contingency planning for the costs associated with possible Medicare coverage of aducanumab.[6] Specifically, CMS is adding approximately $11 per month to the Part B premium to fund an increase in Medicare's contingency reserve.[7] We appreciate that OACT considered a range of scenarios for utilization of this drug, and that CAG purports not to consider the cost of care in its coverage analyses, but it does not make sense for Medicare to increase premiums based on the costs of these drugs while proposing to effectively deny coverage. It is also improper to effectively place blame on beneficiaries with AD for premium increases that affect millions.

- Second, rather than accelerating the development of treatments and improving early diagnosis of AD, the Proposed NCD is delaying treatment and discouraging early diagnosis. Specifically, CMS's requirements for RCTs and "prospective longitudinal studies" would effectively add years to the development process for drugs that have already been subjected to years of rigorous study and analysis. All of the Phase II and Phase III studies for AD mAbs have been at least 18 months in duration, excluding the time it takes to design the study, receive agency approval, enroll sites and patients, and analyze data. Again, absent a clear and automatic path for using existing or ongoing trials to satisfy the possibility of an RCT and

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[4] Letter from Senator Ron Wyden to Secretary Xavier Becerra (December 10, 2021). https://www.finance.senate.gov/imo/media/doc/121021%20Letter%20to%20Sec%20Becerra%20re%20Medicare%20Part%20B%20Premiums.pdf.

[5] *Id*. at 2.

[6] 86 Fed. Reg. 64205, 64209 (November 17, 2021)

[7] Even with broad access to Alzheimer's mAbs we seriously question OACT's assumptions. A premium increase of 14.5% is not justified given the significant self-limiting behavior providers have demonstrated in prescribing aducanumab. This product was approved on June 7, 2021 but only generated $3 million in sales in all of 2021. *See*, Eric Sagonowsky, "After disastrous start to launch, Biogen still expects 'minimal' sales from Aduhelm this year", Fierce Pharma (Feb. 3, 2022). https://www.fiercepharma.com/pharma/after-disastrous-start-to-launch-biogen-expects-minimal-sales-from-aduhelm-next-year

longitudinal study requirement(s), the NCD will add *at least* two additional years of "wait time" for Medicare beneficiaries suffering from AD. Patients with a progressive neurodegenerative disease do not have that time.

- Third, rather than advancing HHS's own National Plan to Address Alzheimer's Disease (the National Plan), CMS is undermining it. On December 27, 2021, HHS published the 2021 Update to the National Plan to Address Alzheimer's Disease.[8] That document, which is required under the NAPA, articulates HHS's official goals with respect to addressing "the many challenges facing people with AD and their families." Goal 1 is to "prevent and effectively treat Alzheimer's Disease and Related Dementias by 2025." However, the Proposed NCD would dramatically limit and delay coverage of all mAbs for all but a small subset of Medicare beneficiaries. This approach is in tension with the strategic pillar for realizing Goal 1 of the National Plan, which requires translation of findings into medical practice and public health programs; CED frustrates this goal.

Irrespective of whether or how CMS finalizes the Proposed NCD, it is clear that HHS should, at a minimum, take a step back and reconsider its holistic approach to AD.

*B. The Proposed NCD is Inconsistent with Congress's Clear Intention to Expedite the Approval and Use of Medicines that Treat Serious, Unmet Medical Needs.*

At around the same time it passed NAPA, Congress was also actively working on the FDA Safety and Innovation Act of 2012 (FDASIA). That act contains multiple amendments to the FDCA that are designed to expedite approval of innovative medicines. Notably, Section 902 of FDASIA establishes the concept of a "Breakthrough Therapy" designation. This provision is nestled between the sections of FDASIA that spell out updates to the "Fast Track" and the Accelerated Approval pathways, reflecting an overall Congressional intent to help ensure that promising treatments for serious conditions are identified earlier in the drug development process and expedited to patients.[9] As Janet Woodcock, Acting Commissioner of FDA, has said, "breakthrough designation" allows the sponsor and the agency to call "all hands on deck" and to rethink the development plan rather than simply proceed through a traditional Phase 1-2-3 process.[10]

In addition, FDASIA also codified and amended FDA's longstanding practice of utilizing an Accelerated Approval pathway. The Accelerated Approval pathway is used by FDA when drugs for serious conditions that fill an unmet medical need are eligible for FDA approval based on surrogate endpoints.[11] To authorize a drug for marketing under Accelerated Approval, FDA must conclude that the surrogate marker is reasonably likely to predict clinical benefit based on the evaluation of

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[8] HHS, Office of the Assistant Secretary for Planning and Evaluation, "National Plan to Address Alzheimer's Disease: 2021 Update" (December 27, 2021). https://aspe.hhs.gov/reports/national-plan-2021-update

[9] See also, FDA's own interpretation of these changes, "The programs described in this guidance are intended to help ensure that therapies for serious conditions are approved and available to patients as soon as it can be concluded that the therapies' benefits justify their risks." https://www.fda.gov/media/86377/download

[10] Lilly announced on June 24, 2021 that its investigational amyloid plaque clearing mAb, donanemab, was granted breakthrough designation. Eli Lilly and Company, Press Release, "Lilly's donanemab receives U.S. FDA's Breakthrough Therapy designation for treatment of Alzheimer's disease." https://www.prnewswire.com/news-releases/lillys-donanemab-receives-us-fdas-breakthrough-therapy-designation-for-treatment-of-alzheimers-disease-301318931.html

[11] FDA, *Accelerated Approval Program*, https://www.fda.gov/drugs/information-health-care-professionals-drugs/accelerated-approval-program

available scientific evidence. Section 901 of FDASIA also made clear that Accelerated Approval should only be granted if FDA can apply the same evidentiary standards of safety and efficacy that FDA applies to traditional new drug and biologic approvals.[12] Lilly and other manufacturers are currently pursuing approval of their investigational anti-amyloid mAbs under this approval pathway.

Taken together, it is clear from the NAPA and FDASIA that Congress wanted speedy options for patients to access drugs for serious conditions with unmet needs, especially people with AD. Sadly, CMS's Proposed NCD with CED requirements would entirely undermine that goal.

*C. The Proposed NCD Is Arbitrary and Capricious, Even Under CMS's Questionable Authority to Condition Coverage on "Evidence Development."*

The Proposed NCD, and its overbroad application to the entire class of monoclonal antibodies directed against amyloid for the treatment of AD, is not only troubling policy, but also contrary to law. If finalized, the NCD will invite legal challenges that could prevent CMS from utilizing its CED process in the future.

The proposed NCD with CED is legally invalid for at least three reasons:

- First, and most fundamentally, CMS lacks the statutory authority for CED. There is nothing in the Medicare statute that authorizes or even mentions CED; it is a construct that CMS invented. In its 2014 "Guidance for the Public, Industry, and CMS Staff: Coverage with Evidence Development," CMS claimed that its statutory authority for CED stemmed from Sections 1862(a)(1)(A) and 1862(a)(1)(E) of the Social Security Act (SSA). But neither provision authorizes CMS to establish any such program. Section 1862(a)(1)(A) requires that an item be reasonable and necessary to diagnose or treat illness or injury. It does not address what may be reasonable and necessary in the very different context of clinical trials. That may be why CMS did not rely on that provision in the proposed NCD with CED here. Section 1862(a)(1)(E), the only statute on which the proposed NCD relies for its CED determination, does not authorize this outcome either. That provision applies in the context of AHRQ research— "in the case of research conducted pursuant to section 1320b–12 of this title." The proposed NCD tellingly offers no explanation of how the clinical trials it contemplates would qualify as "research conducted pursuant to section 1320b-12." Furthermore, HHS's own former General Counsel recognized that a mere note of approval from AHRQ on a CMS proposal to issue an NCD with CED does not suffice.[13] In short, the entire CED construct has no basis in law and CMS lacks statutory authority to impose it.

- Second, even if CMS had statutory authority to impose a CED requirement, the agency has not properly exercised any such authority because it invented CED in purported guidance documents and manual provisions that did not go through notice-and-comment rulemaking. The Supreme Court's *Allina* decision established that the Secretary must use notice-and-comment rulemaking for certain Medicare policies, even in circumstances in which the

[12] Pub. L. No. 112-44 (July 9, 2012), Section 901(a)(2): "It is the sense of Congress that the Food and Drug Administration should apply the accelerated approval and fast track provisions set forth in section 506 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. § 356), as amended by this section, to help expedite the development and availability to patients of treatments for serious or life threatening diseases or conditions while maintaining safety and effectiveness standards for such treatments."

[13] HHS OIG, Advisory Opinion on Medicare Coverage with Evidence Development No. 21-03 (January 14, 2021) (withdrawn).

Administrative Procedure Act (APA) does not otherwise require such rulemaking. Specifically, under Section 1871(a)(2) of the SSA, any Medicare policy that establishes or changes a "substantive legal standard" governing the scope of benefits, payment for services, eligibility of individuals to receive benefits, or eligibility of individuals, entities, or organizations to furnish services must be promulgated through notice-and-comment rulemaking.[14]

The HHS Office of the General Counsel (OGC) interprets the phrase "substantive legal standard" in Section 1871(a)(2) to mean any issuance that: (1) defines, in part or in whole, or otherwise announces binding parameters governing; (2) any legal right or obligation relating to the scope of Medicare benefits, payment by Medicare for services, or eligibility of individuals, entities, or organizations to furnish or receive Medicare services or benefits; and (3) sets forth a requirement not otherwise mandated by statute or regulation.[15]

HHS OGC specifically mentions policies set forth in CMS manuals as an example of setting a "norm" that, under *Allina*, is invalid unless issued through notice-and-comment rulemaking.[16] Likewise, guidance documents that set forth Medicare policies or rules that are not closely tied to statutory or regulatory standards were not validly issued under *Allina*.[17]

CMS's 2014 guidance and its Medicare Program Integrity Manual (where CMS defines reasonable and necessary under §1862(a)(1)(A)) provide the basis for CMS's effort to justify and implement the CED process.[18] Yet neither document was subjected to notice-and-comment rulemaking. As a result, neither document has any legal ability to create or change a standard for Medicare coverage—and yet that is precisely what CMS has attempted to do with CED.

- Third, this NCD with CED is invalid under the APA because it is unreasonably broad in scope and an unexplained departure from previous CMS policy.[19] CMS previously recognized that "FDA approval is a prerequisite for coverage determination" for drug treatments and declined to consider an NCD for drugs that have not yet received such approval.[20] That makes eminent sense, as CMS is not able to evaluate the data supporting an NCD for a drug until that data has been generated in the pivotal trials supporting FDA approval. But here, CMS proposed a sweeping coverage determination without the benefit of evidence regarding other drugs that will fall within the broad class defined by the proposed NCD and without

[14] See *Azar v. Allina Health Servs.*, 139 S. Ct. 1804, 1810 (2019).
[15] HHS OGC Advisory Opinion on Implementing Allina No. 20-05 (Dec. 3, 2020) (citing *Select Specialty Hosp.-Denver, Inc. v. Azar*, 391 F. Supp. 3d 53 (D.D.C. 2019)).
[16] *Id.*
[17] *Id.*
[18] See U.S. Dep't of Health and Human Servs., Centers for Medicare & Medicaid Servs., Guidance for the Public, Industry, and CMS Staff: Coverage with Evidence Development (Nov. 20, 2014), https://www.cms.gov/medicare-coverage-database/view/medicare-coverage-document.aspx?MCDId=27; U.S. Dep't of Health and Human Servs., Centers for Medicare & Medicaid Servs., Medicare Program and Integrity Manual: Chapter 13 – Local Coverage Determinations (Rev. 863, Feb. 12, 2019), https://www.cms.gov/regulations-and-guidance/guidance/manuals/downloads/pim83c13.pdf.
[19] See 5 U.S.C. § 706(2)(A); *Motor Veh. Mfrs. Ass'n v. State Farm Ins.*, 463 U.S. 29, 44 (1983).
[20] See, e.g., U.S. Dep't of Health and Human Servs., Centers for Medicare & Medicaid Servs., CAG-00080N, Venofer: Intravenous Iron Therapy National Coverage Decision (2001), https://www.cms.gov/medicare-coverage-database/view/ncacal-decision-memo.aspx?proposed=N&ncaid=77.

providing any explanation for the scope of that class definition. CMS cannot know yet whether its aducanumab analysis applies to other monoclonal antibody drugs, including donanemab. CMS has not explained why it is appropriate to apply the NCD with CED to the entire class of monoclonal antibodies directed against amyloid for the treatment of AD. Nor did CMS acknowledge its past policy of declining to consider coverage for a drug before it is approved by FDA, let alone explain why it would be justified in reversing that policy here.

If finalized, this proposed NCD with CED would be a sharp departure from CMS's prior policy in an additional important respect: never before has CMS used CED to limit national coverage for an on-label use of a therapeutic drug or biologic already approved by FDA. Even if CMS had some implicit statutory authority to create CED as an alternative coverage paradigm for products or uses not previously reviewed and approved as safe and effective by FDA, CMS lacks any such authority when it comes to a drug that has been approved by FDA for use in the Medicare population and is being considered for coverage for its on-label use. In that situation, the risk that a CED determination will conflict with FDA's prior safety and effectiveness findings is most acute. We recognize that the statutory standard for coverage is phrased slightly differently from the statutory standard for marketing approval. But the proposed NCD reveals that CMS is choosing the CED pathway so it can determine down the road whether aducanumab's "benefits outweigh the risks"—a determination reserved to FDA, and one that FDA has already made. Worse still, CMS is proposing to apply this analysis preemptively to products not yet considered by FDA. It is implausible that Congress intended CMS to create a new paradigm for coverage, not mentioned in any statute, under circumstances where it would conflict with determinations already made by FDA. And the more implausible an agency's assertion of authority, the clearer Congress must be in delegating the authority.[21] It therefore is insufficient that Congress did not explicitly forbid CMS from creating a CED construct; CMS would have to identify clear affirmative statutory authorization, and none remotely exists.

## II. The Proposed NCD with CED Should Not Treat All Monoclonal Antibodies Directed Against Amyloid the Same.

A class-wide coverage decision for anti-amyloid mAbs is unnecessary, premature and lacks patient-centricity. CMS appears to assume that all mAbs are alike. This is not so. There is only one FDA-approved anti-amyloid mAb in the market and the specific regulatory history of that initial product is unlikely to be representative of future product approvals and should therefore not serve as the basis for establishing a national coverage policy. Also, several manufacturers have announced that additional data readouts for their anti-amyloid mAbs are imminent. Specifically, Lilly, Eisai, and Roche/Genentech have all committed to additional readouts in the next 12 to 18 months.[22] At a minimum, CMS should await publication of these data before rushing headlong into a class-wide policy that creates a several year lag in Medicare beneficiary access and stymies innovation.

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[21] See, e.g., *Whitman v. Am. Trucking Associations*, 531 U.S. 457, 468 (2001) (noting it would be "implausible that Congress would give" EPA power to consider costs in setting national air quality standards without a "clear" "textual commitment").

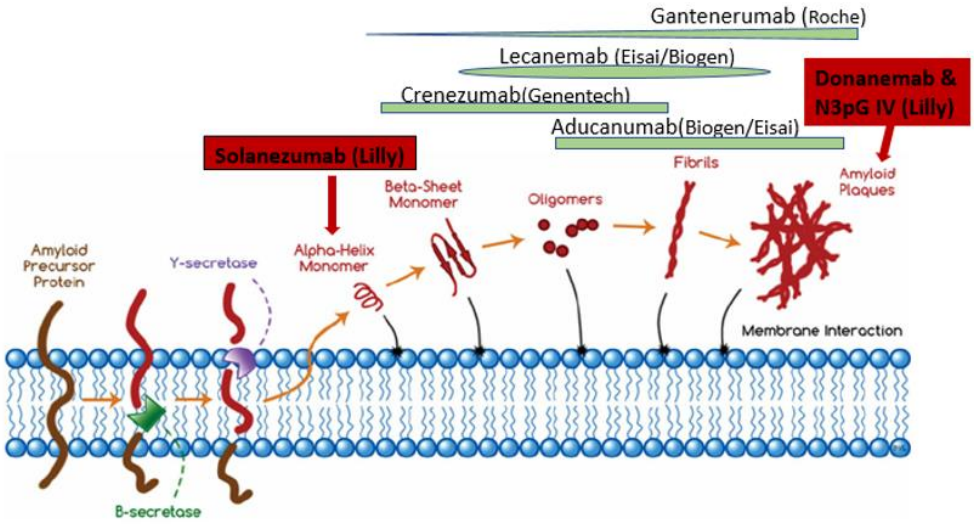
[22] Phil Taylor, *Lilly's and Roche's amyloid-targeted drugs for Alzheimer's diseases*, Fierce Biotech (December 20, 2021)(setting out timelines for various company data disclosures). https://www.fiercebiotech.com/special-report/fierce-biotech-s-top-10-data-readouts-2022-alzheimer-s-drugs

*A. Not all Anti-Amyloid Monoclonal Antibodies Are the Same.*

The Proposed NCD is predicated on the faulty premise that all monoclonal antibodies directed against amyloid are functionally indistinct. This is demonstrably wrong, and each manufacturer seeking to discover and develop an anti-amyloid mAb is investigating a molecule that targets different epitopes (i.e., the part of an antigen molecule to which an antibody attaches itself). The figure below presents, in a very simplistic way, what is known about the basic science behind the creation of amyloid plaques in the brain. For convenience, Lilly has also attempted to characterize (based on public sources) the different epitopes that each product (and manufacturer) is reportedly targeting.

Lilly's solanezumab, for example, targets the Alpha-Helix monomer, an early precursor to amyloid plaque pathology, while other Lilly antibodies (e.g., donanemab and N3pG4) target fully formed, cross-linked deposited amyloid plaques. These biologics are simply not the same products and they do not function in the body in the same way. Other mAbs (e.g., gantenerumab, lecanemab, crenezumab, and aducanumab) target an array of epitopes. Again, it is simply too early to know whether or how these products perform in early AD clinical trials, rendering CMS's "class-wide" analysis woefully premature. Our current understanding of epitope binding among anti-amyloid antibodies is shown in Figure 1.

*Figure 1: Monoclonal Antibodies in Development and Epitope Variations*




But instead of recognizing that the clinical differences are not yet known and that there exists a diversity of anti-amyloid targets, the Proposed NCD proceeds with an "analysis of the evidence" that relies exclusively on Phase III clinical trials that failed to meet their primary endpoints.[23] An analysis that only focuses on the failures would lead to the conclusion there will never be any progress when, in fact, there have been significant advances. Progress is built on learning from these failures, and this is the nature of scientific research—continuous learning to achieve success, often following multiple failures. This type of analysis stacks the deck against emerging therapies like donanemab, which has demonstrated, in a peer-reviewed publication, evidence of improvement in pre-specified

[23] See, Proposed NCD, Evidence Tables 1 and 2.

cognition and functional endpoints in a registration quality Phase II trial.[24] Lilly encourages CMS to abandon its effort to issue a "class-wide" NCD; however, if CMS does not adopt this recommendation it should, at a minimum, revise its evidentiary review to incorporate all relevant data, including published Phase II study results, which are more timely and reflective of the advancement of the science in the field of AD.

*B. CMS's Concerns with Aducanumab Should Not Dictate Restrictions on Coverage for all Anti-Amyloid Monoclonal Antibodies.*

Lilly commends the manufacturer of aducanumab for its contribution to and innovation in the field of AD and for its commitment to advancing the basic science researching the amyloid cascade hypothesis. Discovering cures for significant unmet medical needs is the best and highest calling of the biopharmaceutical industry.

But like all pioneers, the manufacturer of aducanumab suffers from being the first medicine in a challenging and underdeveloped therapeutic area. Lilly fears that CMS, in crafting the Proposed NCD, weighed too heavily the challenges associated with aducanumab. Lilly's program and plans with donanemab are substantially different, as noted below.

*Figure 2: Differences between Aducanumab and Donanemab*

| | Donanemab | Aducanumab |
|---|---|---|
| **Demonstrated Amyloid Plaque Clearance** | ✓ | ✓ |
| **Demonstrated Consistent Clinical Benefit in Cognition/Function** | ✓ | ✗ |
| **Met Prespecified Primary Endpoint in Well Designed Study** | ✓ | ✗ |
| **Published Full Results of Clinical Trial in Peer Reviewed Journal** | ✓ | ✗ |
| **Fully Enrolled Confirmatory Trial with Data Available in Months** | ✓ | ✗ |
| **Therapy Discontinued Upon Amyloid Plaque Clearance** | ✓ | ✗ |

Finally, while we appreciate that cost is not a factor in CMS's coverage decision, it is clear that the initial list price announced for aducanumab generated controversy and consternation.[25] That price has since been significantly reduced and another manufacturer has stated that it will price its anti-amyloid mAb at a price much lower than the original aducanumab price.[26]

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[24] Mintun MA, Lo AC, Duggan Evans C, et al. *Donanemab in Early Alzheimer's Disease*. N. Engl. J. Med. 2021; 384(18):1691-1704. doi:10.1056/NEJMoa2100708

[25] Josh Katz, Sarah Kliff and Margot Sanger-Katz, *New Drug Could Cost the Government as Much as It Spends on NASA*, N.Y. Times (June 22, 2021). https://www.nytimes.com/2021/06/22/upshot/alzheimers-aduhelm-medicare-cost.html; Amy Finkelstein, *That $56,000 Drug? Blame Medicare*, N.Y. Times (August 20, 2021). https://www.nytimes.com/2021/08/20/business/drug-cost-medicare-alzheimers.html

[26] Pam Belluck, *Biogen Slashes Price of Alzheimer's Drug Aduhelm, as It Faces Obstacles*, N.Y. Times (December 21, 2021) https://www.nytimes.com/2021/12/20/health/alzheimers-aduhelm-price.html; Deena Beasley, Roche executive says Alzheimer's drug price will be competitive, Reuters (November 10, 2021). https://www.reuters.com/business/healthcare-pharmaceuticals/roche-executive-says-alzheimers-drug-price-will-be-competitive-2021-11-10/

## III. The Restrictive Coverage with Evidence Development (CED) Requirements of the Proposed NCD Raise Serious Practical, Policy and Ethical Concerns.

In addition to creating significant access barriers to anti-amyloid mAbs, we are deeply concerned that CMS's proposal would undercut FDA's past and, potentially, future determinations regarding the safety and effectiveness of drugs and biologics. CMS's proposal creates significant tension by questioning FDA's judgment and, if finalized, would undermine the substantial, longstanding trust that patients and other stakeholders place in FDA. It also creates an untenable confusion regarding division of responsibilities among the agencies.

### *A. CMS's Proposed Requirements for RCTs are Impractical and Burdensome to Patients and Caregivers.*

Lilly is concerned that the Proposed NCD with CED, which would require a CMS-approved RCT, unnecessarily and inappropriately requires manufacturers to effectively repeat their FDA registration trials but with minor changes to satisfy CMS. The lack of explicit commentary on how registration-quality studies conducted outside of CED will be treated combined with the additional elements of the CED's RCT requirement creates discrepancies that are concerning and require clarification. This is highly impractical, unnecessarily harmful to patients, and inconsistent with CMS's own principles governing application of CED. Indeed, CMS's own principles state "CED will not duplicate or replace the FDA's authority in assuring the safety, efficacy, and security of drugs, biological products, and devices".[27] Lilly has reviewed CMS's "Coverage Criteria for CMS Approved Trials" and has serious concerns regarding these supposed requirements:

- First, as a threshold matter, CMS makes several confusing references to "clinically meaningful improvement." This is not the correct standard for this disease. AD is a degenerative condition and none of the mAbs that target amyloid are being studied to "improve" patient cognition or function (nor would they). The appropriate concept for CMS to consider is "clinically meaningful slowing in the decline of cognition or function." If that phrase is too cumbersome, "clinical benefit" would be a reasonable alternative.

- Second, the Proposed NCD would condition full Medicare coverage on the completion of an RCT that has demonstrated a "clinically meaningful" difference in decline in cognition and function. CMS has indicated that its standard for what constitutes "clinically meaningful" may be "over and above statistical significance." We are concerned that this is a wildly different standard than FDA's "substantial evidence" requirement for approval and that it could take manufacturers several additional years of study to satisfy CMS's requirement for demonstrating a "clinically meaningful" benefit.

  Specifically, Lilly is troubled by CMS's statement that CMS "will use the CDR-SB (Clinical Dementia Rating-Sum of Boxes) to exemplify what constitutes a clinically meaningful benefit in a primary outcome." We do not know what CMS means when it says it will use the CDR-SB to "exemplify" meaningful benefit. ***Does CMS mean that it will require CDR-SB to be the prespecified endpoint?*** If so, that could exclude RCTs that have utilized other highly validated measures of cognition and function, such as the Integrated Alzheimer's Disease Rating Scale (iADRS). Through more than 30 years of history of AD research, Lilly has gained

[27] CMS, Guidance for the Public, Industry, and CMS Staff: Coverage with Evidence Development (2014) https://www.cms.gov/medicare-coverage-database/view/medicare-coverage-document.aspx?MCDId=27

significant experience in the area of scale validation and considers the iADRS to be the most appropriate scale in the assessment of mild cognitive impairment and early AD.

- Third, CMS also suggests that a trial sponsor should demonstrate "a 1-3 point decrease in Mini Mental State Examination, 1-2 point increase in Clinical Dementia Rating Scale sum of boxes, and 3-5 point increase in Functional Activities Questionnaire were indicative of a meaningful decline" and makes reference to a study assessing "minimal clinically important difference" (MCID) in outcomes assessment for Alzheimer's disease. It is important to note that MCID is intended to establish the minimal change over time that an individual would consider meaningful, which is not the same as a meaningful between-group difference in a clinical trial. Rather, experts generally agree that treatment effects of 20% to 30% slowing in progression should be considered clinically meaningful.[28] The duration most ongoing mAb registration trials (usually around 76 weeks) is simply not long enough to demonstrate the effect size that CMS is suggesting. ***Does CMS mean that it will require the point changes identified in this example?***

- Fourth, under "Study Requirements" CMS has stated that the "diversity of patients included in each trial ***must be*** representative of the national population diagnosed with AD." While we applaud this goal and certainly agree that this should be our expectation in all clinical trials over time, it is unrealistic to declare this as a requirement today. Many of the current RCTs to support FDA approval were initiated years ago and patient enrollment already completed, with thousands of patients devoting significant time and commitment to these trials. A goal like this cannot be set retroactively. Instead, progress over time should be recognized and rewarded. Lilly has demonstrated progress in clinical trial diversity over time and has implemented multiple efforts to improve in trial diversity as described later in this letter. It is very important to note there are well documented health system and structural impediments that make it difficult to randomize minority group patients. We also believe that CMS's own requirements limiting the patient population to those without certain comorbidities and conducting RCTs in only hospital outpatient facilities would further undermine any clinical trial sponsor's ability to meet these diversity requirements. ***Does CMS intend for the patient diversity requirement to be aspirational or absolute?***

- Fifth, several of the proposed coverage criteria—specifically (h), (l), or (m)—are unlikely to be reflected in existing FDA registration trial protocols because they were not known (or knowable) to trial sponsors in advance of designing Phase III trials. Specifically, criterion (h), which tautologically requires that "the study has a written protocol that clearly demonstrates adherence to the standards listed here as Medicare requirements," is technically impossible to satisfy for any trial in process because no one could have known what CMS was planning to require. Criteria (l) and (m), which require approved protocols that "explicitly discuss beneficiary subpopulations" and "how the results are or are not expected to be generalizable to affected beneficiary subpopulations," were similarly unknowable. ***How does CMS intend to reconcile its Medicare RCT requirements with FDA accepted protocols for ongoing Phase III trials?***

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[28] Abushakra S, Porsteinsson A, Vellas B, et al. *Clinical Benefits of Tramiprosate in Alzheimer's Disease Are Associated with Higher Number of APOE4 Alleles: The "APOE4 Gene-Dose Effect"*. J Prev Alzheimers Dis. 2016;3(4):219-228.; Insel PS, Weiner M, Mackin RS, et al. *Determining clinically meaningful decline in preclinical Alzheimer disease.* Neurology. Jul 23, 2019;93(4): Vellas B, Andrieu S, Sampaio C, Wilcock G. *Disease-modifying trials in Alzheimer's disease: a European task force consensus*. Lancet Neurol. Jan 2007;6(1):56-62.

Lilly hopes that CMS will heed its own requirement that "[t]he study results are not anticipated to unjustifiably duplicate existing knowledge" (criterion (c) of the "Study Requirements") and address the concerns Lilly has raised above. **Lilly respectfully requests that, if the final NCD retains CED, CMS makes clear that it will accept published FDA registration-quality trials or currently enrolled Phase III confirmatory trials to serve as the basis for satisfying the RCT requirement.** Please see the discussion below for how CMS can accomplish providing this clarity.

*B. The NCD Disproportionately Impacts Communities of Color and CMS's Belief that Health Equity Concerns Will Be Mitigated by CED Is Misguided.*

Lilly views health equity as every individual having fair and just opportunities to be as healthy as possible. This requires removing obstacles to health such as poverty, discrimination, and their consequences, including powerlessness, lack of access to good jobs with fair pay, quality education and housing, safe environments, and health care. Diversity, equity, and inclusion are essential to the modernization of the U.S. health care system to ensure the health outcomes of all people regardless of their sexual orientation, socioeconomic level, regional location, and racial or ethnic background, are improved.

Among our most important racial equity initiatives is our commitment to expanding diversity in Lilly's clinical trial programs. Diverse representation in clinical trials is critical– it helps our researchers understand how effective and safe our medicines may be for those patients who are most likely to take them. That is why it is important for Lilly to enroll a diverse range of people in our AD clinical trials. With respect to AD, our latest clinical trial, TRAILBLAZER-ALZ3 (a trial involving donanemab in asymptomatic AD), utilizes a decentralized clinical trial design in the hope that it will increase diverse enrollment.[29] In addition, we are utilizing our Mobile Research Units[30] so that potential trial participants can complete a screening appointment in a more accessible setting of care. Additionally, we are partnering with key advocacy groups that are developing relationships with community partners. However, these relationships take time to develop and it is unfair to force current patients to await treatment as these structural barriers to representative enrollment are fixed.

However, the issue of fully representative clinical trials is not unique to AD and extends to virtually every other therapeutic area.[31] Even ongoing NIH-funded trials of AD monoclonal antibodies, the very trials that CMS proposes as a second potential pathway for satisfying the Proposed NCD's CED requirements, do not appear to meet the diversity and representation criteria outlined by CMS.[32]

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[29] This study's decentralized approach enables study participation via remote visits and visits away from investigator sites closer to where participants live or work. All cognitive assessments will be conducted remotely by central raters. The goal of this approach is to reach a broader participant group, including more diverse populations, to decrease burden on study locations by requiring less onsite staff to conduct the study, and to maximize convenience for participants. Participants will complete many study activities, including clinical interviews and cognitive testing, via virtual appointments using a study tablet in a convenient location for the participant.

[30] Specialized recreational vehicles, or RVs.

[31] Kennedy-Martin T, et al. *A literature review on the representativeness of randomized controlled trial samples and implications for the external validity of trial results,* Trials (2015;16:495).

[32] Nitzan Arad, et al. *Medicare Coverage of Monoclonal Antibody Treatments for Alzheimer's Disease: Key Issues from the CMS Proposed Coverage Decision*, Duke Margolis Issue Brief (January 2022).

AD is marked by significant health disparities and inequities. Black Americans are nearly two times more likely, and Latinos are 1.5 times more likely to develop AD compared to their White counterparts.[33] Despite this higher risk, Black Americans and Latinos are less likely to receive a timely diagnosis and are more likely to report discrimination as they attempt to access care for AD.[34,35]

While we understand and support CMS's aspiration of ensuring equity and representation in AD studies, CED, especially through RCTs, will not facilitate more representative data or access. At least three requirements in the Proposed NCD, including the CED RCT requirement, the proposed exclusion criteria for approved CED studies, and the limitation of administration of this class to the hospital out-patient setting, will not only exacerbate underlying health disparities in AD, but also unfairly restrict access to this class of medications in minority communities.

- First, CMS's proposal to provide coverage almost exclusively through RCTs is at odds with the well documented underrepresentation in and mistrust of medical research and clinical trials in the Black, Hispanic, Asian, and Native American communities. According to the Alzheimer's Association's Special Report on Race, Ethnicity, and Alzheimer's in America report, more than 60% of Black Americans believe that medical research is biased against minority communities, a view that is largely shared by Asian Americans (45%), Native Americans (40%), and Hispanic Americans (36%).[36]

  These perceptions of bias directly influence interest in participating in clinical trials, with Black Americans being least interested (67%), followed by Asian Americans (73%), Hispanic Americans (78%), and Native Americans (81%).[37] Some of the most common reasons given for being unwilling to enroll in clinical trials include concerns about not wanting to be a "guinea pig," fears that treatment may result in illness, concerns regarding costs, as well as time and transportation implications.[38] Restricting access to anti-amyloid targeted therapies to RCTs will only serve to exacerbate these long-standing fears regarding participating in clinical trials.

  Our concerns that CED will create additional challenges to equity of care in AD are not just theoretical—they are grounded in our direct experience with CED for Amyloid Positron Emission Tomography (PET) scans. Since 2013, the Medicare program has restricted access to Amyloid PET scans through CED.[39] Importantly, NCD 220.6.20 subjects Amyloid PET scans to a *far less restrictive* form of CED relative to this Proposed NCD. These studies, like the IDEAS study (Imaging Dementia Evidence for Amyloid Scanning) and the New IDEAS study,

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[33] Aranda, Maria P., et al. *Priorities for Optimizing Brain Health Interventions Across the Life Course in Socially Disadvantaged Groups*. Florida International University and UsAgainstAlzheimer's. (2019).
[34] Tsoy E, Kiekhofer R.E., Guterman E.L., et al., *Assessment of Racial/Ethnic Disparities in Timeliness and Comprehensiveness of Dementia Diagnosis in California.* JAMA Neurol. (March 29, 2021). https://doi.org/10.1001/jamaneurol.2021.0399
[35] Alzheimer's Association. *Race, Ethnicity and Alzheimer's in America.* (2021). https://www.alz.org/media/Documents/alzheimers-facts-and-figures-special-report.pdf
[36] *Id.* at 2.
[37] *Id.*
[38] *Id.*
[39] CMS, NCD Beta Amyloid Positron Tomography in Dementia and Neurodegenerative Disease (220.6.20).

demonstrate the extent to which even less restrictive CED requirements hinder minority access to critical AD care.

As CMS knows, the original IDEAS study, despite enrolling over 18,000 participants, faced significant challenges enrolling a representative patient population- the same requirement that is outlined in the Proposed NCD and included in CMS's 2014 CED Guidance. As a result, the administrators of IDEAS, the American College of Radiology and the Alzheimer's Association, developed a new study protocol designed specifically to measure the impact of amyloid PET scans in a more diverse patient population. New IDEAS is designed to enroll a total of 7,000 Medicare beneficiaries with the goal of at least half of participants self-identifying as Black/African American (at least 2,000 participants) and Latino/ Hispanic (at least 2,000 participants).[40,41]

To support the goal of diverse enrollment, New IDEAS study team retained minority recruitment centers of excellence who could bring best practices and specific recruitment strategies to engage underrepresented populations, including partnerships with community members and healthcare providers in select metropolitan areas to encourage Black/African American and Latino participation.[42] Notwithstanding a concerted effort to recruit a majority diverse patient population, as of January 2022, only 18% of study participants identified as Black, Hispanic, or Latino.[43]

It stands to reason that CMS's proposal to restrict coverage to RCT CED, which again, is a *far more restrictive form of CED*, will result in even lower participation, and therefore minimal access to anti-amyloid targeted therapies in minority communities. Indeed, this hypothesis is born out in a systematic review of ongoing clinical trials for AD and related dementias, which found that Latino and Black Americans make up less than 10% of clinical trial participants.[44]

As we work to achieve the goal of fully representative trials, patients should not, in the meantime, be subject to unrealistic and unobtainable requirements in order to receive Medicare coverage for FDA-approved therapies.

- Second, we are concerned that the exclusion criteria outlined in the Proposed NCD are at odds with CMS's requirement that trials supporting CED must be representative of the "national population diagnosed with AD". Specifically, the Proposed NCD requires approved protocols to exclude patients that have "any neurological or other medical condition other than AD that may significantly contribute to cognitive decline" and "medical conditions, other than AD, likely to increase adverse events." [45] Several conditions would disqualify patients from enrolling in RCTs based on these draft parameters, including cardiovascular disease and uncontrolled diabetes, which are not only more prevalent in communities of color, but also

[40] Alzheimer's Association. *Race, Ethnicity and Alzheimer's in America.* (2021) at 2.
[41] New IDEAS Study Protocol, *New IDEAS: Imaging Dementia—Evidence for Amyloid Scanning Study NCT04426539* (ClinicalTrials.gov). https://www.ideas-study.org/Getting-Started/Protocol.
[42] *Id.*
[43] American College of Radiology, *New IDEAS Study Update.* (January 26, 2022).
[44] National Institute on Aging, *Development of an NIA Practice-Based Research Network to Conduct Alzheimer's and Related Dementias Clinical Research.* (2021).
[45] Proposed NDC at 26, 28, and 55.

associated with higher dementia risk.[46,47] Indeed, a recently published systematic review of AD trials found that eligibility criteria that excluded individuals with psychiatric illness (78.2%), cardiovascular disease (71.3%) and cerebrovascular disease (68.3%) "may have led to a disproportionate exclusion of ethnoracially diverse individuals" in those trials evaluated by researchers.[48] This conflict further underscores how inappropriate and unrealistic CED is to achieving greater health equity in AD. In addition, the proposed exclusion criteria may also limit access among other populations of patients, including those with Down syndrome and Dominantly Inherited Alzheimer's Disease (DIAD). These conflicts further underscore how inappropriate and unrealistic CED is to achieving greater health equity in AD.

Indeed, the Proposed NCD's inclusion and exclusion criteria may conflict with the FDA's guidance on Enhancing the Diversity of Clinical Trial Populations, which notes that sponsors should "work to ensure that eligibility criteria serve the goal of having a representative sample of the population for whom the drug has been developed and examine each exclusion criterion to determine if it is needed to help assure the safety of trial participants or to achieve the study objectives. If it is not needed, consider eliminating or modifying the criterion to expand the study population."[49]

- Third, by requiring all trials to occur in the hospital outpatient setting, the Proposed NCD will exacerbate geographic and socioeconomic disparities and underlying issues of trust regarding the medical community. Geographically, we believe that access to academic medical centers (AMCs), which will be the facilities most capable of administering RCTs, remains limited for disadvantaged populations.[50] Moreover, unequal access to "high-quality health facilities, including AMCs, is recognized as a contributor to racial and ethnic health disparities."[51] We appreciate that CMS is motivated by concerns for patient safety to limit any RCT to the hospital outpatient setting. However, FDA expressly considered and declined to impose this requirement or any other form of risk evaluation or mitigation strategies (REMS).

  Limiting access to the entire class of anti-amyloid therapies to the hospital outpatient setting will also exacerbate existing socioeconomic disparities that exist in communities of color. Time, cost, and an inability to obtain transportation are all self-reported barriers to enrolling in AD clinical trials.[52] The proposed framework for CED will likely create additional hardship for certain patients, such as those more reluctant to enter clinical trials or those who live further away from outpatient centers that are participating in CMS-approved studies. For example, millions of Medicare beneficiaries reside in rural parts of the country and many lack the resources to travel. As CMS itself has noted, "rural Americans often experience longer travel times to reach their healthcare practitioners and frequently lack access to public

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[46] Alzheimer's Association, *Race, Ethnicity and Alzheimer's in America*. (2021).
[47] Susane Franzen, et al., *Diversity in Alzheimer's disease drug trials: The importance of eligibility criteria,* Alzheimer's and Dementia, The Journal of Alzheimer's Association (September 2021). https://doi.org/10.1002/alz.12433.
[48] *Id.*
[49] FDA, *Enhancing the Diversity of Clinical Trial Populations — Eligibility Criteria, Enrollment Practices, and Trial Designs Guidance for Industry* (November 2020).
[50] Roosa Sofia Tikkanen, et al., *Hospital Payer and Racial/ethnic Mix at Private Academic Medical Centers in Boston and New York City*, Int J Health Serv. (July 2017).
[51] *Id.*
[52] Alzheimer's Association, *Race, Ethnicity and Alzheimer's in America* at 5. (2021).

transportation, which can impede timely access to necessary care."[53] These barriers are likely to extend to caregivers, who often must balance the potential loss of wages and reduced time for other familial responsibilities, with the decision to support their loved ones in AD clinical trial enrollment.[54]

## IV. To Fix the Proposed NCD, CMS Must Provide Automatic Coverage for On-Label Use Where Confirmatory Data Demonstrate a Slowing in Decline of Cognition and Function.

Lilly does not support the Proposed NCD with CED. We believe that CMS should instead finalize an NCD that provides for Medicare coverage of all anti-amyloid mAbs in a core covered patient population where robust confirmatory data are available. To underscore how targeted and principled Lilly's proposal is, consider the text below revising CMS's current proposal:

> *The Centers for Medicare & Medicaid Services (CMS)* ~~***proposes to***~~ ***will*** *cover FDA approved monoclonal antibodies directed against amyloid for the treatment of Alzheimer's disease (AD)* ***for the FDA-indicated patient population where confirmatory data demonstrates a statistically significant reduction of clinical decline in a pre-specified, validated primary outcome measure of cognition and function****.* ***All other uses of FDA approved monoclonal antibodies directed against amyloid for the treatment of AD will be covered*** *under Coverage with Evidence Development (CED) in CMS approved randomized controlled trials* ***or in CMS approved longitudinal studies,*** *or in trials supported by the National Institutes of Health (NIH).* ~~***All trials must be conducted in a hospital-based outpatient setting.***~~

We believe this approach responds to the urgent need for patients to access effective treatments while addressing many of the shortcomings described above.

### *A. Automatic Coverage for On-Label Use Upon Availability of Substantial Evidence of Clinical Benefit Is Consistent with Congress's Desire to Accelerate Access to Patients.*

To align CMS's NCD with the National Plan, CMS should grant automatic coverage for the relevant FDA-approved indications and patient populations as quickly as substantial evidence of clinical benefit becomes available. Recall, the National Plan envisions the rapid deployment of "effective treatments." Confirmatory data of an anti-amyloid mAb demonstrating a statistically significant slowing of decline in cognition and function satisfies this standard. The National Plan also calls for "translating findings into medical practice and public health programs." Lilly submits that there is no more self-evident and obvious way to satisfy this goal than by promptly covering demonstrably effective treatments so that innovative products are available in a timely manner for providers and patients.

Automatic coverage would also allow the NCD to evolve as FDA-approved labeling or significant changes to the literature evolve, without requiring CMS to continuously revisit the NCD through multiple, time-consuming reconsideration processes. In particular, drugs would be covered for the

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[53] CMS, *Improving Health in Rural Communities FY 2021 Year in Review* (2021). https://www.cms.gov/files/document/fy-21-improving-health-rural-communities508compliant.pdf.

[54] Krishnoo K. Indorewalla, et al., *Modifiable Barriers for Recruitment and Retention of Older Adults Participants from Underrepresented Minorities in Alzheimer's Disease Research*, Journal of Alzheimer's Research (2021).

clinical stage of disease identified in the FDA-approved indication statement, e.g., for currently available therapies and therapies anticipated to become available in the next year, this is early AD (MCI or mild dementia stage of disease). Utilizing language specific to FDA-approved indication statements, rather than specific stages of disease, is important, as it allows for variability in indication statements at both launch and as they evolve over time. There is inadequate evidence today to cover these drugs in later stages of disease (moderate / severe AD) or earlier stages (pre-symptomatic disease) but evolving evidence could support broader indication statements in the future. This approach also would end coverage once patients reach a more advanced clinical stage than described above, when treatment should be stopped.

*B. Automatic Coverage for On-Label Use Upon Availability of Substantial Evidence of Clinical Benefit Eliminates the Confusion of FDA's Role and Demonstrates Coordination Across Federal Agencies.*

Congress, taxpayers, patients, and providers are not interested in interagency turf battles and NAPA clearly requires HHS to improve coordination across agencies. Yet, as drafted, CMS's Proposed NCD effectively negates FDA's approval authority and purports to supplant FDA's expertise with CMS's own desire to generate and evaluate data to apply to an ill-defined "reasonable and necessary" standard. Aside from whipsawing patients, this creates a dangerous precedent whereby CMS freely substitutes its own judgment for FDA's. Based on our review of prior NCDs, we believe this is a stark departure, as CMS has never before denied coverage for on-label use of a therapeutic drug deemed safe and effective for the Medicare population by FDA.[55]

However, if CMS and FDA work together by consulting and aligning on the best interpretation of confirmatory data as it becomes available, CMS would cure a major defect of the Proposed NCD. Automatic coverage in the face of confirmatory data would demonstrate that HHS is committed to bringing coherence to a comprehensive regulatory framework, not piecemeal evaluation where one standard is good enough to "market" a drug or biologic, but a different standard applies to whether Medicare pays for it.

Furthermore, by conditioning approval on the availability of "substantial evidence"—a legal concept relevant to FDA approval—CMS would be *aligning* its efforts with FDA's rather than working at cross-purposes against FDA. Specifically, substantial evidence was addressed in the Food and Drug Administration Modernization Act of 1997 (FDAMA) (Pub. L. 105–115), which stated that such a standard would serve as the requirement for establishing effectiveness either through two adequate and well-controlled trials or by a single trial plus confirmatory evidence. FDA has a clear interpretation of this standard and has developed guidance documents and protocols to ensure that the standard is faithfully applied.[56]

By aligning its coverage policy with FDA approval standards, and potentially coordinating with FDA in their review of any confirmatory data, CMS can demonstrate that it is heeding the dictates of NAPA while also satisfying is obligations to cover reasonable and necessary items and services for Medicare beneficiaries.

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[55] Cathy Kelly, *Medicare, Alzheimer's Drugs And The Single Payer Effect*, InVivo (November 9, 2021) https://invivo.pharmaintelligence.informa.com/IV124933/Medicare-Alzheimers-Drugs-And-The-Single-Payer-Effect

[56] See, e.g., FDA, *Draft Guidance, Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products Guidance for Industry,* (December 2019).

*C. Automatic Coverage for On-Label Use Upon Availability of Substantial Evidence of Clinical Benefit Better Aligns with CMS's Statutory Authority and the Principles of Appropriate Administrative Process.*

The entire evidentiary basis for CMS's "class-wide" determination is that "no trial has convincingly demonstrated a clinically meaningful improvement in health outcomes…"[57] However, the minute this statement becomes false, CMS's entire analysis becomes unsupportable. With several data readouts imminent in the next 12 to 18 months, CMS would be well served to craft an NCD that can automatically adjust to new data. And even if CMS believes that it enjoys broad statutory flexibility or that its decisions are exempt from challenge under the APA (a position we question), the agency must still follow the dictates of the Medicare statute and cover items or services that are "reasonable and necessary." In the face of substantial evidence demonstrating a product slows decline in cognition and function, CMS's objections to coverage are moot. Continued reliance on the analysis in the evidentiary sections would be a textbook case of arbitrary and capricious conduct, as CMS would be knowingly relying on a stale and incomplete analysis. Any legal challenge to CMS on these facts would almost certainly result in a reversal and remand of the NCD and could undermine CMS's ability to use CED in the future. This can be easily avoided if automatic coverage to label is contemplated and written into the NCD.

*D. Automatic Coverage for On-Label Use Upon Availability of Substantial Evidence of Clinical Benefit Recognizes and Encourages Innovation and Product Differentiation.*

CMS justifies its decision to apply a "class-wide" coverage policy by stating "anti-amyloid mAbs as a class…have a similar function of reducing amyloid in the brain."[58] That is woefully reductive and completely minimizes potentially meaningful differences in mechanisms of action, protein structures being targeted, patient groups being studied, and dosing regimens. An ironclad CED that adds years to any manufacturer's development program is certain to discourage additional investment and innovation and could further seriously delay meaningful advances in the treatment of AD. In contrast, an adaptable coverage policy that ensures timely access to proven therapies will encourage further research and development in this area of critical need.

## V. To Improve the NCD, CMS Should Clarify that CED Requirements Do Not Duplicate FDA Registration Trials and CED Should Supplement, Not Restrict, Coverage.

Lilly appreciates that the population of people with AD is heterogeneous and that the nature of AD and Alzheimer's related dementias are varied. We are committed to continuing to develop evidence of safety and efficacy in our products by studying various subgroups and by testing treatments at different points in the progression of AD. Lilly will doubtlessly continue to prove how its products work outside the clinical trial setting and for patients not covered by the existing population. However, these efforts should not require repeating clinical trials used to support a product's FDA approval, nor can they be the vehicle to provide access to the medicine for the labeled population. As noted in previous sections, CMS should provide full coverage for the labeled population. CMS should only use CED (if appropriate at all) to encourage data development that is additive to the existing body of scientific knowledge by encouraging novel and supplemental research aims.

[57] Proposed NCD at 23.
[58] *Id*. at 8.

*A. Any Requirement for an RCT Under CED Must Make Clear that Published FDA Registration Trials or Enrolled Confirmatory Trials Demonstrating Substantial Evidence Would Satisfy CMS Requirements.*

CMS requirements for RCTs covered by Medicare may be incompatible with the protocols for FDA-supported ongoing clinical trials designed to demonstrate meaningful clinical benefit for people with AD. We do not believe it is (or ought to be) CMS's intention to second-guess the FDA when it comes to clinical trial design, nor do we believe it is ethical or appropriate to randomize patients to a placebo, an effective treatment, or best supportive care where an approved therapeutic with demonstrated clinical benefit is available and is the standard of care. To that end, CMS must explicitly state that a manufacturer's published registration-quality trials or enrolled confirmatory Phase III trials would satisfy CMS's RCT requirements. Similarly, and for the reasons set forth above, certain other criteria that foreclose the use of ongoing Phase III trials as sufficient to fulfill CED requirements must be revised. Notably, the requirement that a study meet the (not yet finalized) Medicare trial requirements or specific requirements related to subgroup analysis are almost certain to be absent from the trial protocols from ongoing trials.

We recommend CMS retain for itself greater flexibility in the method by which the agency supports clinical trials by adopting more permissive language and making it clear to stakeholders that Phase III or Phase IV trials designed to support FDA-approval obligations would satisfy CMS's requirements by making the following textual changed to the Proposed NCD:

> *(c) Study* ~~***Requirements***~~ ***Design Recommendations***
>
> ***Phase III or IV clinical trials designed and carried out to support FDA-approval would satisfy these study design requirements.*** The diversity of patients included in each trial ~~**must**~~ ***should*** be representative of the national population diagnosed with AD.
>
> Additionally, any CMS approved trial ~~**must**~~ ***should*** adhere to the following standards of scientific integrity:

*B. Any form of CED Must Provide Greater Clarity and Flexibility Around Longitudinal Studies.*

Longitudinal studies—including the use of patient registries—should exist as a stand-alone CED option that provides a bridge to automatic coverage rather than as an additional barrier to coverage after a product has demonstrated efficacy in an RCT or other clinical trial. But that is not the current proposal. Presently, the Proposed NCD states that CMS "may extend" an RCT "to a prospective longitudinal study when the RCT is completed." This feels arbitrary as CMS has made no effort to explain when or why it will (or will not) require conversion of an RCT into a longitudinal study; nor has CMS prespecified any stopping point for completing such a study and moving an anti-amyloid therapy out of CED and into full coverage. The current text suggests a perpetual limbo for patients, providers, and manufacturers who are left only to hope that eventually CMS's concerns as to the long-term effectiveness of the studied therapeutic will be satisfied. That result is troubling.

Moreover, the Proposed NCD implies that only longitudinal studies emanating from CMS-approved RCTs would be CED-eligible. This is a self-defeating limitation that serves no purpose. CMS should, instead, retain maximum flexibility to encourage a variety of longitudinal studies by expressly committing to coverage where these studies explore new uses, new patient populations, or new sites of care. CMS has several options: it could cover longitudinal studies that grow out of CMS's approved

RCTs and *other* clinical trials; it could cover longitudinal studies that are unconnected to any clinical trials; or it could cover use by Medicare beneficiaries enrolled in patient registries and for which manufacturers, academics, government agencies or other qualified parties have committed to answering novel research questions. CMS should cover all of these options.

Finally, CMS should consider coverage for manufacturer supported longitudinal studies and real-world evidence studies. Lilly believes that establishing donanemab's ability to effect clinically meaningful delays in cognitive and functional decline in our registration trials will represent a monumental advance in the care of people with AD. Nevertheless, our evidence generation plans do not end with the demonstration of the short-term efficacy and safety.

While there is reason to believe that these benefits will translate into longer-term clinical, humanistic and societal benefits, we appreciate the critical need to generate evidence to support these beliefs. To this end, Lilly has begun work on a robust real world evidence research plan which we hope to initiate upon achieving donanemab approval. This plan includes one or more prospective, longitudinal studies in which we will follow donanemab-treated patients and appropriate controls for an extended period of time—perhaps 5 to 10 years—in order to establish a variety of long-term treatment benefits. As these studies will be "pragmatic" in nature, we intend to broaden study entry criteria relative to our clinical trials and include care sites reflective of real-world practice so as to ensure enrollment of a fully representative patient population and permit examination of outcomes across important patient subgroups.

We are committed to measuring outcomes of interest that include not only slowing of cognitive and functional decline over an extended time horizon, but additional downstream benefits important to patients, their caregivers and to payers, such as decreased patient dependency and caregiver burden, improved patient and caregiver quality of life, and decreased healthcare system costs. Our hope is to design and implement these studies in partnership with healthcare systems that share our desire to accelerate change in the AD care ecosystem so as to deliver cutting-edge care to AD patients as soon as possible. We would be willing to share our study design concepts with CMS at an appropriate time and entertain any suggestions that would lead to studies that better address our common evidence needs.

If covered by CED, CMS would be providing meaningful encouragement for all of these forms of longitudinal data development. We reiterate the relevant portion of the proposed textual change to the NCD and that would add longitudinal studies as a standalone CED option:

> ***All other uses of FDA approved monoclonal antibodies directed against amyloid for the treatment of AD will be covered*** *under Coverage with Evidence Development (CED) in CMS approved randomized controlled trials* ***or in CMS approved longitudinal studies,*** *or in trials supported by the National Institutes of Health (NIH).*

*C. Any Form of CED Must Address the Disparities in Health Equity Created by the Proposed NCD.*

As described elsewhere in this letter, CMS's Proposed NCD serves to exacerbate, rather than ameliorate, disparities in health outcome in several ways. As CMS works to finalize the NCD, we encourage the agency to take the following steps:

- First, CMS must clarify its diversity requirements for patient trial selection. Lilly shares the goal of designing clinical trials that represent the racial and ethnic and other dimensions of

difference observed in a particular disease state and works very hard to achieve it. Yet there are several well-documented structural impediments to recruiting diverse patients for participation in research and real-world evidence studies. For example, there is real mistrust from experiments like the Tuskegee Syphilis Study or the lack of consent obtained by researchers when using Henrietta Lacks' cells that have led many minority group members to be wary of clinical trials. There is also limited awareness of trial opportunities among potential participants, barriers preventing patient access to trials, like inconsistent transportation, lack of access to broadband/internet, or lack of childcare, and a lack of existing clinical trial sites in underrepresented communities.

- Second, CMS should abandon its proposal that trials must take place in the hospital outpatient setting by striking this requirement from the proposed coverage statement. The hospital outpatient requirement creates serious risks for exacerbating health equity issues by limiting available clinical trial sites by creating additional hardship for certain patients, such as those more reluctant to enter clinical trials or those who live further away from outpatient centers that are participating in CMS-approved studies. As mentioned above, millions of Medicare beneficiaries reside in rural parts of the country and many lack the resources to travel. As CMS itself has noted, "rural Americans often experience longer travel times to reach their healthcare practitioners and frequently lack access to public transportation, which can impede timely access to necessary care."[59]

- Third, CMS must also relax its criteria related to patient eligibility in any RCT (or longitudinal study) as some of these criteria are likely to add to existing access barriers. Specifically, CMS has proposed excluding patients with comorbidities that may significantly contribute to cognitive decline or are likely to increase significant adverse events. This criterion is likely to eliminate a significant number of patients with AD from eligibility, as patients with dementia are more likely to have multiple health conditions. A 2019 study conducted in the United Kingdom showed that 22% of dementia patients had three or more comorbidities and 8% had four or more comorbidities, compared to 11% and 3% respectively in all patient groups. Between 17 and 20% of dementia patients had a diagnosis of stroke or depression, which could contribute to cognitive decline.[60] This criterion is also harmful to inclusive clinical trial design. Four in 10 Americans have two or more chronic conditions, conditions which also disproportionately impact communities of color.[61]

**VI. CMS Must Provide Greater Coverage for Diagnostics.**

Regardless of the approach CMS takes in the NCD, it is critical that beneficiaries have access to amyloid PET to support the identification of the most appropriate patients for treatment and to monitor their response to treatment. Lilly appreciates that CMS has articulated within the Proposed NCD the important role that amyloid PET plays in patient identification, but further action is necessary in order to optimize patient care. As drafted, the Proposed NCD is myopic and will be out-

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[59] CMS, *Improving Health in Rural Communities FY 2021 Year in Review.* https://www.cms.gov/files/document/fy-21-improving-health-rural-communities508compliant.pdf.

[60] Public Health England, *Dementia: Comorbidities in Patients Data Briefing* (November 2019). https://www.gov.uk/government/publications/dementia-comorbidities-in-patients/dementia-comorbidities-in-patients-data-briefing#:~:text=Patients%20with%20dementia%20are%20more,in%20the%20all%20patient%20group.

[61] CDC, *Prevalence of Multiple Chronic Conditions Among US Adults, 2018 Research Brief*. (September 2020). https://www.cdc.gov/pcd/issues/2020/20_0130.htm

of-date immediately upon either the FDA approval of a mAb that includes a requirement for patient monitoring in the FDA-approved label or any mAb that is covered outside of the CED.

In order to optimize patient care, CMS should revise the anti-amyloid therapeutic NCD to establish outright coverage for Aβ PET for beneficiaries with a clinical presentation consistent with the stage of disease identified in the FDA approved indication statements for anti-amyloid therapy who are being evaluated for diagnosis and potential treatment or continuation of treatment with an FDA-approved anti-amyloid therapeutic, regardless of the type of coverage for the therapeutic. In addition to appropriate patient identification, as CMS has acknowledged, evaluating amyloid levels during the course of treatment with an amyloid-reduction therapy, as was performed in Lilly's TRAILBLAZER-ALZ trial, likely results in both clinical and fiscal responsibility by reducing the purchase and administration of unnecessary doses. Thus, CMS should not limit Aβ PET to one scan per patient. Rather, Aβ PET should be covered according to the indication statements on both Aβ PET and the anti-amyloid therapeutic, which may include Aβ PET scans as a condition of monitoring or as part of therapy continuation instructions. Additionally, we should expect that many people may need more than one amyloid PET scan in their lifetime as they age and the risk of AD increases.

If CMS is too limited in their ability to change the Aβ PET NCD from within the construct of the anti-amyloid therapeutic NCD, then CMS should make incremental improvements to the Proposed NCD and then initiate reconsideration on an expedited basis or retirement of the NCD for Beta Amyloid (Aβ) PET in Dementia and Neurodegenerative Disease (NCD 200.6.20). If so, we urge CMS to revise the Proposed NCD to cover amyloid PET in one of two ways: (1) "consistent with the amyloid PET indication statement when utilized within approved anti-amyloid therapeutic CED studies", or (2) "consistent with the protocol design of a CMS-approved anti-amyloid therapeutic CED study."

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In conclusion, Lilly appreciates this opportunity to present our comments on the Proposed National Coverage Analysis (NCA) for Monoclonal Antibodies Directed Against Amyloid for the Treatment of Alzheimer's Disease. We are hopeful about the future of Alzheimer's care, and we urge CMS to revise its proposed coverage policy to allow timely and appropriate access to new amyloid-targeting therapies as well as to the diagnostic tools that are necessary to identify patients who could most benefit from these therapies. We appreciate the time CMS has dedicated to meeting with us and other stakeholders, and we would be happy to answer any questions you have about these comments. Please contact Adam Phipps at phippsad@lilly.com or 614-256-6099 to discuss this letter.

Sincerely,

Anne E. White
President, Neuroscience Business Unit, Eli Lilly and Company