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hhc
human health care

February 9, 2022

VIA ELECTRONIC SUBMISSION

Tamara Syrek Jensen
Director, Coverage and Analysis Group
Center for Clinical Standards and Quality
Centers for Medicare and Medicaid Services
7500 Security Boulevard
Baltimore, Maryland 21244-1850

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

Dear Ms. Jensen:

Eisai Inc. ("Eisai" or "the Company") is pleased to submit these comments to the Centers for Medicare and Medicaid Services (CMS or "the Agency") on the Proposed Decision Memorandum for Monoclonal Antibodies Directed Against Amyloid for the Treatment of Alzheimer's Disease (CAG-00460N) ("proposed Decision Memo"). Eisai is deeply concerned about the long-term restrictions on access to treatment for people with Alzheimer's disease contemplated by CMS' proposal to apply Coverage with Evidence Development (CED) to all monoclonal antibodies in this class. We view the sweeping determination that anti-amyloid plaque drugs categorically are not reasonable and necessary and the application of an onerous CED through a National Coverage Determination (NCD) for investigational therapies that are not approved by the Food and Drug Administration (FDA) as both arbitrary and without precedent, as it prejudges clinical trial data and labeling. **We urge CMS to reconsider the impact of this proposal on people with Alzheimer's disease, their families, and caregivers and finalize an NCD that limits coverage for the class, *without CED,* to beneficiaries with mild cognitive impairment (MCI) or mild dementia due to Alzheimer's disease, with confirmed presence of amyloid in the brain.**

Our comments focus on why CED is not reasonable, necessary, or appropriate for the class or our investigational monoclonal antibody lecanemab, for which Phase 3 data are anticipated to read out *only months following finalization of the NCD*, as well as our broader policy concerns, including that the NCD as currently framed would discriminate against people with Alzheimer's disease as compared to other diseases, such as cancer and HIV/AIDS. We also express concern regarding the proposed use of CED where CMS has not reviewed the evidence for lecanemab or identified insufficiencies in the data that would support use of CED. The proposed Decision Memo's lack of evidence review or scientific explanation for including lecanemab fails to provide stakeholders with an adequate opportunity to provide meaningful comments in response to the proposed Decision Memo. We also wish to convey our legal concerns with CMS' proposed NCD.

I. EISAI'S *human health care* MISSION IN ALZHEIMER'S DISEASE

Eisai is driven by our "*human health care*," or *hhc*, mission in Alzheimer's disease. Everything we do is guided by the principle that patients and their families come first, and we have a responsibility to listen and learn from them. Eisai has been listening, aligning, and understanding the needs of patients living with Alzheimer's disease since well before the approval of our first Alzheimer's disease therapy. This core principle began at Eisai more than 30 years ago and continues to drive our focus on patients, their families, and the public. This principle is a central tenet throughout our response to the initiation of the National Coverage Analysis (NCA) and the proposed Decision Memo.

Eisai's efforts to discover new treatments for Alzheimer's disease began in the early 1980s through the Company's relentless pursuit to understand the underlying causes of the disease. The Company has spent over a quarter of a century with people affected by this disease to better understand their needs. Eisai's pioneering efforts in Alzheimer's disease led to the landmark approval of the anti-Alzheimer's agent Aricept® (donepezil) in 1996, after nearly 13 years of research and development work.[1]

These efforts have led to continued Alzheimer's disease therapy breakthroughs, and discoveries, including our investigational monoclonal antibody, lecanemab. On September 28, 2021, Eisai announced initiation of a rolling submission to the FDA of a Biologics License Application (BLA) for lecanemab for the treatment of early Alzheimer's disease. The BLA is proceeding under the Accelerated Approval pathway and is primarily based on clinical, biomarker, and safety data from the Phase 2b clinical trial (Study 201) in people with early Alzheimer's disease and confirmed amyloid pathology. We expect to complete this rolling submission in the first half of calendar year 2022. Additionally, Eisai completed enrollment of 1,795 patients in the lecanemab confirmatory Phase 3 CLARITY AD clinical trial, which is expected to report out in the Fall of 2022.

The FDA granted lecanemab Breakthrough Therapy designation in June of 2021, based on findings from a Phase 2b clinical trial and its long-term extension exploring the impacts of lecanemab on reducing brain amyloid-beta (Aβ) and clinical decline. In December of 2021, the FDA also granted lecanemab Fast Track designation.

Scientific and technological breakthroughs have led to the advancement of new biomarker-guided, targeted pathway-based medicines. The Company looks forward to engaging with CMS and other stakeholders throughout this process to ensure coverage is available to the right patients at the right time in accessible settings of care, as well as coverage of the most modern and up-to-date methods of confirming amyloid, including coverage at this time for follow-up positron emission tomography (PET) scans and other necessary diagnostic tests to guide patient treatment. This is an area where technology is rapidly evolving and coverage flexibility is critical.

II. RECOMMENDATION FOR FINAL DECISION: EISAI URGES CMS TO FINALIZE NATIONAL COVERAGE WITHOUT A CATEGORICAL CED REQUIREMENT

Eisai strongly opposes CMS' proposal to apply CED categorically to all monoclonal antibodies directed against amyloid for the treatment of Alzheimer's disease. Application of CED through a NCD for investigational therapies that are not yet approved by the FDA is both arbitrary and without precedent, as it prejudges clinical trial data and labeling. Eisai is deeply troubled that CMS not only proposes to apply CED to these future therapies, but to require the strictest type of CED in the form of randomized controlled trials (RCTs), with treatment restricted to hospital-based outpatient settings.

In the case of our investigational humanized monoclonal antibody, lecanemab, CED is not reasonable, appropriate, or necessary based on the findings from our Phase 2b study and open label extension (OLE), as well as the short timeline to anticipated traditional approval. The Phase 2b study of lecanemab published in 2021 demonstrated that lecanemab cleared amyloid plaques in a dose- and time-dependent manner and slowed cognitive decline in early Alzheimer's disease.

Eisai has expressed support for an NCD that limits coverage to beneficiaries with MCI or mild dementia due to Alzheimer's disease, with confirmed presence of amyloid in the brain. We cannot support a proposal that would severely restrict Medicare beneficiary access for the foreseeable future to all drugs in this class, exacerbate health inequities, and not account for important ongoing research. We are further concerned that this action directly calls into question FDA's role in determining safety and efficacy, as well as the agency's regulatory autonomy and scientific independence.

Our concerns about CMS' CED proposal are set forth in further detail below. Eisai urges CMS to finalize an NCD that does not categorically limit monoclonal antibody treatments to CED, but rather leaves open the option for broader availability of promising FDA-approved therapies. CMS has at its disposal a robust claims database for surveilling and analyzing health benefits of drugs within the Medicare program over time; manufacturers also leverage this data for the same purposes, as Eisai is planning on doing in its lecanemab CLARITY AD trial.

III. CED PROPOSAL CONTAINS SCIENTIFIC AND ANALYTIC LIMITATIONS REGARDING THE CLINICAL EVIDENCE

There are significant scientific and analytic limitations to the clinical evidence CMS considered, as well as the systematic review and meta-analysis conducted by scientists at the National Institute on Aging (NIA) to advocate for the CED. In particular, the evidence review does not acknowledge recent Phase 2 clinical trial data from monoclonal antibodies with robust amyloid clearance, which support amyloid as a surrogate reasonably likely to predict clinical benefit.[2] These data, together with the aducanumab analyses, support that high levels of amyloid reduction are required for clinical benefit. In Evidence Table 2 of the proposed Decision Memo, all of the treatments – except aducanumab – did not robustly remove amyloid because of the drug target/mechanism (preference for targeting Aβ monomers and not plaques [solanezumab]; lack of microglial activation for plaque clearance [crenezumab]) or underdosing (bapineuzumab; gantenerumab Scarlett Road studies;

current gantenerumab Phase 3 studies are testing a four-fold higher dose). Based on the totality of data and a careful, sophisticated dose-response analysis of amount of amyloid reduction and effect on Clinical Dementia Rating, sum of boxes (CDR-SB), the FDA concluded that "there is a clear relationship between reduction of amyloid-beta plaque burden in brain and preserving of clinical function in the aducanumab program, which is consistent across all 6 other available programs of anti-Aβ antibodies under development over the past decade."[3]

Moreover, CMS proposes for the CED studies to determine whether monoclonal antibodies directed against amyloid to treat Alzheimer's disease "result in both a statistically significant and clinically meaningful difference in decline in cognition and function." No Medicare laws, regulations, or guidance, however, specifically require evidence that a drug results in "meaningful improvement in health outcomes" to satisfy Medicare's statutory reasonable and necessary criteria.[4]

The *minimal clinically important difference (MCID)* attempts to quantify "the smallest difference in score in the domain of interest which **patients** perceive as beneficial and would mandate . . . a change in the patient's management."[5] This definition involved two constructs: 1) a minimal amount of patient reported change and 2) something significant enough to change patient management. Hence, the potential usefulness of MCID is to serve as a benchmark for improvement of individual patients, and through change in clinical parameter (*e.g.*, disease state or severity). The success of treatment would then be measured by the proportion of patients who reach MCID as opposed to the average change of a group of patients.[6] Consequently, the change in scores depends on the patient's initial baseline status. The proposed NCD, however, fails to take patient centricity into account.

The study by Andrews et al. (2019)[7] is a retrospective database study utilizing data collected from the NACC initiative. The clinical meaningfulness thresholds were not derived from randomized treatment comparisons, but rather from within group changes over time. The assessment of clinical improvement is not performed by patients; the reliability and consistency of clinical adjudications by different physicians/clinics may require further evaluation. In addition, instead of a definitive clinically important change score, the analysis resulted in an "average score" for the group. Patients may vary significantly from each other and although they may fall within the average score, whether that finding was specifically appropriate for them is questionable.[8] In essence, an MCID is required to function as a measure of responsiveness of a given instrument. Andrews et al. (2019) reported the proportion of patients who reached MCID in this study, albeit assessed by clinicians not patients. The minimum change thresholds at which over 70% of visits were classified as having a clinically meaningful decline measured by CDR-SB was, in fact, an increase of 0.5 for the whole sample evaluated in the study without separating out disease status or severity.

Finally, Eisai is highly concerned and fundamentally disagrees with CMS' perspective that the causal pathway is not sound. The science, from our perspective and from that of our partners at the National Institutes of Health, is sound and robust, including extensive product-specific data as well as ongoing discoveries that further reinforce the key relationship of the amyloid pathway with tau, neurodegeneration, and clinical decline. Our investment in and dedication to this area of research and the millions of people suffering from this debilitating disease are built on this strong foundation.

IV. CED IS NOT REASONABLE, NECESSARY, OR APPROPRIATE FOR LECANEMAB OR THE CLASS

Institution of CED for lecanemab and the entire class of monoclonal antibody therapies to assess the association between clearance of amyloid and slowing of cognitive decline would be duplicative of data that manufacturers are already generating. Eisai's Phase 2b data on lecanemab shows that the mechanism of action allows for robust clearance of amyloid, associated with a slowing of clinical decline, as specified in further detail below. Eisai views application of CED for lecanemab as not reasonable, appropriate, or necessary based on this Phase 2b data on slowing of clinical decline, combined with a low rate of amyloid related imaging abnormalities (ARIA), *and* data from the anticipated completion of the confirmatory Phase 3 trial, which was designed to provide the robust evidence of clinical efficacy, which will be available *within months of the conclusion of the NCA*.

A. Rolling BLA Submitted in September with Phase 3 Data Read-out Anticipated in Fall 2022

Lecanemab is an investigational humanized monoclonal antibody that selectively binds to neutralize and eliminate soluble, toxic amyloid-beta aggregates (protofibrils) that are thought to contribute to the neurodegenerative process in Alzheimer's disease. The FDA granted lecanemab Breakthrough Therapy designation in June of 2021, based on findings from a Phase 2b clinical trial and its long-term extension exploring the impacts of lecanemab on reducing brain amyloid-beta and clinical decline. On September 28, 2021, Eisai announced initiation of a rolling BLA submission, which is proceeding under the Accelerated Approval pathway and is primarily based on clinical, biomarker, and safety data from the Phase 2b clinical trial (Study 201) in patients with early Alzheimer's disease and confirmed amyloid pathology. On December 20, 2021, FDA granted lecanemab Fast Track designation.

Eisai completed enrollment of 1,795 patients in the confirmatory Phase 3 CLARITY AD clinical trial, and the Phase 3 clinical study, AHEAD 3-45, is currently exploring lecanemab's safety and efficacy in individuals with preclinical Alzheimer's disease. The Phase 3 study (CLARITY AD) in early Alzheimer's disease patients will report out in the Fall of 2022 and serve as a confirmatory study for these findings. Based on this anticipated timeline, full data on the efficacy and safety of lecanemab will be available only months after conclusion of the NCA. There is no scientific reason for a CED to apply to lecanemab under these circumstances.

September 2021	Fall 2022	December 2022
Rolling BLA submission	Anticipated Phase 3 Study (CLARITY AD) read-out	Anticipated submission for traditional FDA approval

CMS states in its own Guidance for the Public, Industry, and CMS Staff on the use of CED: "[W]e do not contemplate the application of CED to drugs or biologics that have not been approved by FDA for at least one indication."[9] Eisai would have significant concerns about CMS instituting CED requirements for lecanemab in any case, but particularly prior to FDA making an approval

decision on the drug. This type of action would be precedent-setting for the biopharmaceutical industry and raise significant concerns about pre-judgment of clinical trial data and FDA approval. If CMS later determines that a drug in this class is not reasonable and necessary once data are available, CMS has the authority to initiate a CED proposal at that time; the current time is not ripe for this type of determination.

B. Phase 2b Data Demonstrated that Lecanemab Cleared Amyloid Plaques in a Dose- and Time-dependent Manner and Slowed Clinical Decline in Early Alzheimer's Disease

The Phase 2b study of lecanemab was published earlier in 2021 and demonstrated that lecanemab cleared amyloid plaques in a dose- and time-dependent manner and slowed clinical decline in early Alzheimer's disease. The Phase 2b clinical efficacy results are consistent across endpoints and statistical methodology, including the primary Bayesian statistical analyses.[10] New clinical and biomarker data also are now available from the double-blind phase and OLE of the lecanemab Phase 2b study.[11]

In the double-blind phase, after 18 months of treatment at the highest dose of 10 mg/kg administered intravenously (IV) biweekly, 81% of early Alzheimer's disease patients became amyloid negative by visual read of the amyloid PET scan, with corresponding changes in biomarkers of amyloid (plasma Ab42/40) and tau (plasma p-tau181), and 30% slowing of clinical progression by the ADCOMS composite scale. This dose reduced amyloid by approximately 70 CL from a mean baseline of 74.5 CL (94% reduction) at 18 months.[12] The extent of reduction in amyloid and corresponding biomarker changes were correlated with slower cognitive decline at the treatment group and patient levels, consistent with amyloid being a surrogate outcome measure reasonably likely to predict clinical benefit.

The OLE was initiated after analysis of the core double-blind period. Individuals were started on lecanemab 10 mg/kg IV biweekly after a period of 9-59 months off-treatment (mean 24 months). The clinical and biomarker treatment effect of lecanemab at the end of the double-blind phase was maintained while off-treatment during the gap period, consistent with a disease-modifying effect.

Initiation of lecanemab treatment in the OLE confirmed that lecanemab produces a robust clearance of brain amyloid, with significant amyloid reduction as early as three months, and >80% of subjects achieving amyloid negative status as early as 12 months.

Consistent with the safety findings in the core period, lecanemab was well-tolerated with <10% incidence of ARIA-E at 10 mg/kg biweekly in the Core and OLE. The incidence of symptomatic ARIA-E was <2% in Core and OLE. This safety profile enables lecanemab to be initiated at the therapeutic dose without titration.

These results reinforce and expand upon the unique clinical and biomarker profile of lecanemab. The mechanism of action allows for robust clearance of amyloid, associated with a slowing of clinical decline. Because of the low rate of ARIA, an adverse event associated with amyloid targeting therapeutics, the therapeutic dose may be initiated without the need for titration.

The clinical and biomarker effects in the OLE suggest a disease-modifying effect, and the potential for further benefit with maintenance treatment even after amyloid is cleared, which can be monitored by blood-based biomarkers.

C. Lecanemab Phase 2b Study and Phase 3 Study Design Satisfy Draft CED Criteria

Requiring CED as a condition of coverage is not reasonable in the case of lecanemab, as the Phase 2b data and Phase 3 study design already satisfy the main draft CED criteria. A side-by-side comparison of these studies against CMS' proposed CED criteria is set forth in the Appendix. Given that the lecanemab Phase 2b and Phase 3 studies already satisfy the CED criteria, there is no basis for requiring that post-FDA-approval use of the drug be limited to CED.

Our research findings will answer the questions that CMS proposes for inclusion in CED-related RCTs and detail findings in population subgroups. There are no scientifically sound or reasonable policy grounds for requiring further RCTs or prospective longitudinal studies for this class to re-assess these questions and examine safety and efficacy in a manner that exceeds FDA requirements for approval, particularly in a progressive, degenerative, and fatal disease like Alzheimer's disease. Once a drug has demonstrated efficacy in a Phase 3 clinical trial, to the satisfaction of FDA experts, leading to traditional approval, there is no longer a need to perform additional clinical trials with placebo. Indeed, imposing such a requirement for an already proven therapy poses serious ethical concerns.

With the confirmatory data for lecanemab anticipated to be available in the Fall of 2022, treating physicians and the broader Alzheimer's disease community will be well-equipped with information to make determinations on appropriate use of lecanemab, along with reference to expert clinical practice guidelines. In addition, NCD specifications limiting coverage to beneficiaries with MCI or mild dementia due to Alzheimer's disease, with confirmed presence of amyloid in the brain, along with Medicare Administrative Contractor (MAC) claims review, will aid in ensuring treatment is made available and covered only for beneficiaries for whom treatment is appropriate.

D. Lecanemab's Phase 3 Trial is Representative of the National Population

In further alignment with the CED proposal, our CLARITY AD trial patient population provides a good representation of the United States (U.S.) Medicare population. The distribution of Medicare beneficiaries by race/ethnicity in 2019 was 75% White, 10% Black, 9% Hispanic, 4% Asian, <1% American Indian, and the remaining percentage is "Multiple Races."[13] Of CLARITY AD's enrolled U.S. population, approximately 22.5% are Hispanic, 4.5% are Black, .7% are Asian, .1% are American Indian or Alaskan Native, and .1% are Native Hawaiian or Other Pacific Islander, resulting in a total diverse population of ~25% (2.1% of subjects are both Black as well as Hispanic, therefore the total rate is less than the sum of the individual race and ethnicity rates), aligning with the total diverse Medicare population. Race and age are included as subgroups for demographics and adverse events in the CLARITY AD protocol, with an analysis of these subgroups detailed in the Statistical Analysis Plan.

Inclusion of diverse patient populations in clinical trials may lead to more robust and complete data that increase the understanding of racial and ethnic differences in treatment responses that, in turn, may contribute to reduced disparities in health and outcomes of care. However, despite major efforts by the FDA and other organizations, diversity in clinical trials has not substantially improved. This is not limited to Alzheimer's disease clinical studies. Researchers have identified five critical barriers to participation of racially and ethnically diverse patient populations: mistrust; lack of comfort with the clinical trial process; lack of information about clinical trials; time and resource constraints associated with participation; and lack of awareness about the existence and importance of clinical trials and medical interventions.[14]

Institution of a CED program likely will exacerbate these barriers. Lower participation by race/ethnicity has been reported in many therapeutic areas, including but not limited to oncology, diabetes, systemic lupus erythematosus, and, most recently, vaccines.[15]

E. Proposed Decision Memo Fails to Follow Procedures Necessary for Triggering CED

In addition to the multiple grounds set forth above for not applying CED to lecanemab, the proposed Decision Memo fails to discuss lecanemab's data or identify any insufficiency in available evidence, which is a critical requirement for CMS to trigger use of CED pursuant to Section 1862(a)(1)(A), (E) of the Social Security Act (SSA). It is not clear how CMS reached a determination as to the appropriateness of application of CED to lecanemab or whether the lecanemab data were reviewed prior to proposing to apply CED to control coverage of lecanemab upon FDA approval. This lack of evidence review fails to provide adequate notice to the public and a meaningful opportunity to comment or respond to the proposed Decision Memo.

In addition, CMS erred by requiring anti-amyloid plaque drugs to meet an unlawfully heightened burden of proof. The statute excludes from coverage only those items and services that are "not reasonable and necessary for the diagnosis or treatment of illness or injury."[16] However, in the proposed Decision Memo, CMS presumes that FDA-approved drugs in this class are not safe and effective, and therefore not reasonable and necessary, requiring affirmative "evidence sufficient to conclude that the use of monoclonal antibodies directed against amyloid for the treatment of Alzheimer's disease improves health outcomes for Medicare beneficiaries[.]"

In its proposed Decision Memo, CMS failed to adequately explain how it reconciles its conclusions with its own prior policies and FDA's decision to approve ADUHELM® (aducanumab-avwa). CMS' conclusion that the evidence is insufficient to show that anti-amyloid monoclonal antibodies are safe and effective for the treatment of Alzheimer's disease contradicts FDA's contrary conclusions across this range of medicines, in contravention of CMS' existing coverage policies – and FDA's conclusions still are more favorable for lecanemab. Lecanemab is Breakthrough-designated, meaning that FDA has determined that even "preliminary clinical evidence indicates that the drug may demonstrate substantial improvement on a clinically significant endpoint(s) over available therapies."[17]

CMS' policy, set out in the Medicare Benefit Policy Manual, is that "[d]rugs or biologicals approved for marketing by the Food and Drug Administration (FDA) are considered safe and

effective for purposes of [the reasonable and necessary] requirement when used for indications specified on the labeling." Medicare Benefit Policy Manual, Chapter 15, § 50.4.1; *Porzecanski v. Azar*, 316 F. Supp. 3d 11, 14 (D.D.C. 2018) ("Drugs approved by the Food and Drug Administration (FDA) are considered reasonable and necessary when used for indications specified on their FDA-approved labeling." (citing the Manual)). That policy applies to ADUHELM because it is an FDA-approved drug under the definition in the Manual. Drugs and biologicals with approved new drug applications (NDAs) are considered FDA-approved. *See* Medicare Benefit Policy Manual, Chapter 15, § 50.4.1 (acceptable evidence of FDA-approval is "[a] copy of the FDA's letter to the drug's manufacturer approving the new drug application (NDA)"). CMS has a duty to explain why it is not following *its own policy* of treating FDA-approved drugs as safe and effective with respect to ADUHELM and other anti-amyloid plaque drugs.[18] Unfortunately, the proposed NCD does not discuss the reason for this change in CMS policy.

Thus, CMS also erred by failing to defer to FDA's finding that anti-amyloid plaque drugs, including aducanumab and Breakthrough-designated investigational products, such as lecanemab, are in fact likely to be safe and effective, and indeed may demonstrate a substantial improvement on clinically significant endpoints over available therapies. The statutory scheme requires CMS to adopt FDA determinations of safety and effectiveness; CMS, in turn, evaluates whether or not the product is reasonable and necessary for the Medicare population in light of FDA's finding. CMS erred by failing to defer to FDA's findings.

V. POLICY CONCERNS WITH PROPOSED DECISION MEMORANDUM

A. CED Should Not Apply to Investigational Therapies

Application of CED to future anti-amyloid monoclonal antibodies in development, prior to FDA approval or labeling, is arbitrary and unprecedented. The proposal to apply CED to these therapies appears to be made based on an unsupported assumption that all drugs in the class have a similar function of reducing amyloid in the brain. This assumption is not sufficient for reaching a categorical conclusion that data findings will be alike across the entire class and, as such, that it is appropriate to institute a significantly restrictive and onerous coverage requirement now that will apply for the foreseeable future to all therapies in development.

The proposed Decision Memo's application of findings from failed clinical trials for the first generation of anti-amyloid monoclonal antibodies (*e.g.*, bapineuzumab and solanezumab) to lecanemab and other second-generation agents is unscientific. The proposed Decision Memo incorrectly integrates data from these first-generation drugs in the Evidence Tables. For example, some of the data included are from registries rather than RCTs and are not representative of current therapies. The medical community has identified myriad factors that led to the failure of earlier potentially Alzheimer's disease-modifying agents, such as: the agent's failure in attaining robust and selective target engagement in the brain; starting treatment at a clinical stage that is too late to be effective; underpowered trials; adverse side effects on cognition; and flawed trial execution.[19]

As Dr. Dennis Selkoe states in a recent article comparing second-generation antibodies against amyloid accumulation (*e.g.*, aducanumab, lecanemab, gantenerumab, and donanemab) to first-

generation agents, the current antibodies "unambiguously clear amyloid deposits from brain regions that are important for cognition and this effect is accompanied by a variable 20 to 40% slowing of cognitive decline in 18-month trials. Collectively, these data represent the closest the Alzheimer's disease field has come to a disease modifying approach."[20]

The proposed Decision Memo makes a broad brushed determination that these drugs – as a class – are not reasonable and necessary, and then contemplates arbitrarily applying CED treatment to these investigational therapies prior to availability of data used for FDA approval or labeling, and continuing the CED after Accelerated Approval and even after traditional approval is received based on findings from these wholly different first-generation therapies. This CED, like those preceding it, can be expected to last many years and continue without a specific end date, to the severe detriment of Alzheimer's disease patients awaiting access to this next generation of therapies.

B. CMS' CED Proposal Will Severely Limit and Delay Beneficiary Access to Treatments

Institution of CED requirements for anti-amyloid monoclonal antibodies would pose a high burden for investigators and severely restrict access for Medicare beneficiaries for whom treatment is appropriate, only a small proportion of whom will be able to receive treatment. Eisai estimates the early Alzheimer's disease patient population in the U.S. is approximately 1 million persons. Even with a clinical trial of 10,000 patients, which is several times larger than a typical trial, only ~1% of eligible beneficiaries would receive treatment with a particular drug. Multiplying this across the class of potentially included drugs still results in a very small subset of eligible patients receiving treatment.

Eisai urges CMS to carefully consider the serious concerns raised on these access points in comments from beneficiaries with Alzheimer's disease and their caregivers. For example, as Voices of Alzheimer's emphasizes, "Beyond broadly restricting Aduhelm, [CMS'] requirement that successive Alzheimer's 'mab' medications, regardless of their own merits, be classified in the same restrictive category is unconscionable. We are dying from this disease, and yet [CMS'] bureaucratic gobbledygook would deny us access to successive Alzheimer's disease modifying therapy."[21] Patient groups also have raised concerns regarding the discriminatory nature of the proposed CED's exclusion of certain patients with Alzheimer's disease who also have other conditions, such as Down Syndrome.

In addition to broad access issues, we also are concerned that this CED will drive significant inequalities in drug access to FDA-approved therapies. Restricting coverage to a CED construct and limiting treatment to hospital-based outpatient settings will result in concentration of available treatment centers in limited geographic areas and compound inequities for patients lacking resources or support to travel for treatment. If therapies are only covered in a RCT versus standard of care, then some proportion of patients will presumably be randomized to placebo and, thus, not have the opportunity for benefit despite the existence of FDA-approved therapy. As a result, the proposal *de facto* prioritizes non-Medicare patients with the means to pay out-of-pocket for treatment. In addition, the timeline for CED structures to be ready for enabling patient treatment will result in delays in treatment for patients, which is particularly concerning for a

neurodegenerative, fatal disease where time is of the essence.

Eisai is concerned about application of even less rigorous forms of CED, such as a registry, based on our collective experience with registries in other contexts. Registries can be slow to launch, limit enrollment and access, and be highly expensive. Eisai always gathers real world data on safety and efficacy after drugs are approved, but we do not support a coverage decision that so severely limits coverage and access.

Eisai also is troubled that the CED proposal does not provide an expedited, pre-specified mechanism for ending applicability of CED to therapies satisfying CMS outcomes thresholds. The lengthy CED process set forth in the proposal (*i.e.*, RCT converting to longitudinal study, followed by a reconsideration request) will result in continued delays in access for the majority of Medicare patients with Alzheimer's disease. In the case of lecanemab, it will not drive data generation, as the necessary data generation is already underway; it will only serve to add administrative burdens and restrict access.

Treating physicians, under the guidance of clinical practice guidelines, will have access to lecanemab data – including full data shortly after the NCA concludes – for purposes of making determinations as to whether treatment is appropriate for a particular patient. These treating physicians, along with the Medicare MACs, should serve as the gatekeepers to treatment with lecanemab to provide uniform access to beneficiaries regardless of where they live or their nearness to a treatment center. Access to lecanemab also should not be affected by the timeliness with which external structures and processes are in place for CED to be in operation or the number and location of enrolled providers.

C. Use of CED for Newly Approved Drugs is Against CMS' Principles & Duplicates FDA Processes

According to CMS' guiding principles in its Guidance for the Public, Industry, and CMS Staff on the use of CED for newly approved biologicals, CED is not to be used to "duplicate or replace the FDA's authority in assuring the safety, efficacy, and security of drugs, biological products, and devices.[22] The proposed Decision Memo further states that CED study results must not be "anticipated to duplicate existing knowledge." Eisai anticipates read-out of Phase 3 data in Fall of 2022 for lecanemab and a subsequent decision on traditional approval. CMS should not duplicate procedures long entrusted by Congress solely to the FDA's purview through application of CED to lecanemab.

We separately have grave concerns about the potential use of CED in a way that undermines the Accelerated Approval pathway or duplicates the role of the FDA in assessing innovation. In the case of ADUHELM, the first new drug approved for the disease in nearly 20 years, Eisai is concerned that CMS is attempting to use CED and this NCD process to circumvent the role of the FDA and its jurisdiction in determining safety and efficacy of new drugs. Approval of a drug through the FDA's Accelerated Approval pathway requires companies to complete Phase 4 confirmatory trials. If the trial does not verify the drug's anticipated clinical benefit, then it is within the authority of the FDA to remove the drug from the market. CMS should not duplicate procedures already in effect through the FDA and under the FDA's purview.

The proposed Decision Memo disregards the fact that the Accelerated Approval pathway is intended to provide approval of drugs *based on surrogate endpoints*, with a confirmatory trial providing further evidence thereafter. With the exception of the confirmatory trial, Accelerated Approval is intended to operate in all other respects in the same way as a traditional approval. It is not meant to confer inferior status to an Accelerated Approval therapy. Accelerated Approval is meaningless if CMS limits coverage to RCTs. While reimbursement would be provided in the context of the trial, it is as if the approval had not occurred at all from an expanded patient access perspective. This outcome cannot be what Congress intended in establishing the Accelerated Approval pathway.

The proposal's treatment of Accelerated Approval also creates a problematic fissure in evidentiary standards between CMS and the FDA, which Eisai urges CMS to correct. As Dr. Sean Tunis noted:

> [F]ederal law provides the FDA with authority to grant accelerated approval for [monoclonal antibody (mAb) therapies], while the same evidence falls short of meeting CMS interpretation of its reasonable and necessary authority. Importantly, by the FDA's evidentiary standards, all drugs approved through accelerated approval would fail to meet CMS's evidence requirements as articulated in the draft [monoclonal antibody] NCD.[23]

We encourage consideration of risks that CMS' action in disregarding the purpose of the Accelerated Approval pathway here could be precedent-setting in this and other disease states. This decision may result in companies not pursuing Accelerated Approval in the future to the detriment of patients or, in a worst-case scenario, holding commercial availability of a drug until a Phase 3 trial is complete, as a way to ward against the long-term impacts of a CED. It also threatens to usurp the role of the FDA as the arbiter and expert on which drugs to accelerate through FDA review.

It is unclear to stakeholders in the Alzheimer's disease community why Alzheimer's disease treatments are the only accelerated drug treatments that are receiving such potentially restrictive coverage that undermines this devastating and fatal disease and discriminates against people with Alzheimer's disease. We urge CMS to carefully consider comments from across the Alzheimer's disease community during this process and rethink this decision.

VI. CONCLUSION

Eisai appreciates the opportunity to comment on the proposed Decision Memo. We urge CMS to finalize an NCD that limits coverage for the class, *without CED*, to beneficiaries with MCI or mild dementia due to Alzheimer's disease, with confirmed presence of amyloid in the brain. We request careful consideration of the rationale and data supporting a finding that CED is not appropriate or necessary for lecanemab. Eisai further requests that CMS consider the severe restrictions the CED would pose for Medicare beneficiary access for the foreseeable future to all drugs in this class.

We would be pleased to answer any questions about these comments and look forward to working with CMS on ensuring uniform and equitable access to therapy for patients with Alzheimer's disease.

Sincerely,
/s/
Lynn D. Kramer, MD, FAAN
Chief Clinical Officer, Neurology Business Group
Eisai Inc.

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APPENDIX

Study 201 and CLARITY AD Satisfy the Proposed CED Requirements

	Study 201 (Phase 2b)	CLARITY AD (Phase 3)	CMS CED
Study Design	A Placebo-Controlled, Double-Blind, Parallel-Group, Bayesian Adaptive Randomization Design and Dose Regimen-finding Study with an Open-Label Extension Phase	A Global, Placebo-controlled, Double-blind, Parallel-group, Randomized Trial with Open-label Extension	Randomized controlled trial…extended to a prospective longitudinal study
Population	MCI due to AD or mild AD dementia (NIA-AA criteria, CDR 0.5-1) • Confirmed amyloid pathology (amyloid PET or CSF) • MMSE 22-30 • Memory impairment (WMS-IV LMSII ≥1 SD below age-adjusted mean)		*(a)Patient Criteria* Patients must have: • A clinical diagnosis of . . . MCI due to AD or mild AD dementia; and • Evidence of amyloid pathology consistent with AD
	SELECTED EXCLUSIONS • Any neurological condition that may be contributing to cognitive impairment above and beyond that caused by the participant's AD • Any other medical conditions which are not stably and adequately controlled, or which in the opinion of the investigator(s) could affect the participant's safety or interfere with the study assessments		Patients must not have: • Any neurological or other medical condition (other than AD) that may significantly contribute to cognitive decline • Expected death from any cause during the duration of the study • Medical conditions, other than AD, likely to increase significant adverse events
Treatment	DOUBLE-BLIND PHASE (18 month treatment) • Lecanemab 2.5 mg/kg, 5 mg/kg, or 10 mg/kg IV every 2 weeks (LEC2.5BW, LEC5BW, LEC10BW) • Lecanemab 5 mg/kg, or 10 mg/kg IV every 4 weeks • Placebo OPEN LABEL EXTENSION • Lecanemab 10 mg/kg IV every 2 weeks • Planning to incorporate: (1) Biomarker-guided transition to less frequent maintenance dosing schedule	DOUBLE-BLIND PHASE (18 month treatment) • Lecanemab 10 mg/kg IV every 2 weeks • Placebo OPEN LABEL EXTENSION • Lecanemab 10 mg/kg IV every 2 weeks • Planning to incorporate: (1) Biomarker-guided transition to less frequent maintenance dosing schedule; and (2) subcutaneous dosing later this year	
Primary Outcome	Change from baseline in ADCOMS (Composite scale: cognition and function) at 12 months of treatment	Change from baseline in the CDR-SB (Global scale; cognition and function) at 18 months of treatment	*(b) Research Questions* CMS approved trials must address, at a minimum, the research questions below:

	• LEC10BW versus placebo: 64% probability of super-superiority to placebo[1] 98% probability of being superior to placebo[1] 30%[1] less decline relative to placebo, (frequentist: p=0.027 [2]) Effects sustained in GAP period off-drug prior to OLE		• Does use of monoclonal antibodies directed against amyloid for the treatment of AD result in a statistically significant and clinically meaningful difference in decline in cognition and function?
Secondary Outcomes	• Global: ADCOMS at 18 months LEC10BW - 30% less decline, p=0.034 [2] • Cognitive: ADAS-cog14 at 18 months LEC10BW - 47% less decline, p = 0.017 [2] • Global: CDR-SB at 18 months LEC10BW - 26% less decline, p = 0.125 [2]	• Cognitive: ADAS-cog14, MMSE • Functional: ADCS-ADL-MCI • Global: ADCOMS	
Biomarker Outcomes	• Amyloid PET: Dose and time dependent reduction of amyloid as early as 3 months. >80% amyloid negative by visual read at 18 months. • CSF: Reduction of CSF p-tau • Blood: Dose and time dependent increase in Ab42/40 ratio and decrease in p-tau • Effects sustained in GAP period off-drug prior to OLE	• Imaging: amyloid PET, tau PET, volumetric MRI • Blood and CSF, including: Aβ[1-42], neurogranin, NFL, t-tau, and p-tau	
Safety Assessment	• Overall rate of TEAE SAE: Similar incidence to placebo • ARIA-E: Dose related increase (9.9% for LEC10BW; 14.3% in APOE4 carriers) • Infusion related reactions: Dose related increase (19.9% LEC10BW, most mild-moderate)	• AE, SAE, labs, EKG, VS, CSSR-S, safety MRI • AEs of special interest – ARIA-E, ARIA-H, infusion related reactions	• What are the adverse events associated with the use of monoclonal antibodies directed against amyloid for the treatment of AD?
Sample Size	• 854 randomized • In U.S., 3.1% Black, 5.4% Hispanic	• >90% power to detect >0.37 treatment difference in CDR-SB at 18 months • 1,795 randomized • In U.S., 4.5% Black, 22.5% Hispanic	*(c) Study Requirements* The diversity of patients included in each trial must be representative of the national population diagnosed with AD

Table definitions: MCI, mild cognitive impairment; AD, Alzheimer's disease; MMSE, Mini-Mental State Exam; WMS-IV LMSII, Wechsler Memory Scale IV-Logical Memory (subscale) II; SD, standard deviation; CDR-SB, Clinical Dementia Rating, sum of boxes; TEAEs, treatment emergent adverse events; PET, positron emission topography; CSF, cerebrospinal fluid.

[1] Bayesian Analysis: Primary analysis was super-superiority over placebo by ≥25% at 12 months. Goal was 80% probability of ≥25% reduction in decline versus placebo for early progression to Phase 3.
[2] Traditional MMRM Analysis.