

THE AMERICAN GERIATRICS SOCIETY 40 FULTON STREET, 18TH FLOOR NEW YORK, NEW YORK 10038 212.308.1414 TEL www.americangeriatrics.org

January 18, 2022

Steven D. Pearson President Institute for Clinical and Economic Review 14 Beacon Street, Suite 800, Boston, MA 02108

Re: Draft Scoping Document for Beta-Amyloid Antibodies for Early Alzheimer's Disease

Dear Mr. Pearson:

The American Geriatrics Society (AGS) greatly appreciates the opportunity to comment on the draft scoping document outlining the assessment of beta-amyloid antibodies for the treatment of Alzheimer's disease (AD). The AGS is a nationwide, not-for-profit society of geriatrics healthcare professionals dedicated to improving the health, independence, and quality of life of older people. Our 6,000+ members include geriatricians, geriatrics nurse practitioners, social workers, family practitioners, physician assistants, pharmacists, and internists who are pioneers in advanced-illness care for older individuals, with a focus on championing interprofessional teams, eliciting personal care goals, and treating older people as whole persons. The AGS believes in a just society, one where we all are supported by and able to contribute to communities where ageism, ableism, classism, homophobia, racism, sexism, xenophobia, and other forms of bias and discrimination no longer impact healthcare access, quality, and outcomes for older adults and their caregivers. The AGS advocates for policies and programs that support the health, independence, and quality of life of all of us as we age.

We applaud the Institute for Clinical and Economic Review (ICER) for engaging stakeholders to refine the scope of the assessment of donanemab and lecanemab for the treatment of early AD. The AGS also supports a reassessment of aducanumab to update ICER's evidence review should new clinical evidence emerge. Given the heavy toll of AD on patients, caregivers, and their families, it is crucial to evaluate the clinical evidence of these treatments and their safety and effectiveness thoroughly.

The AGS appreciates the opportunity to review this draft scope and share our recommendations which we hope you will consider as you move through the process of developing the evidence report and presentation.

GENERAL COMMENT

The AGS recommends a revision of the fifth line on the second page, "...accumulate betaamyloid in the brain, which can be detected in the cerebrospinal fluid (CSF)," which implies that individuals with AD have higher levels of beta-amyloid in the brain detected in the CSF. However, the levels of beta-amyloid are lower in the CSF for people with AD as the disease progresses.^{1,2}

COMMENTS ON PICOTS

Populations

The AGS recommends greater granularity in the sociodemographic factors for subpopulations, particularly in age and race/ethnicity in order to assess the level of diversity, equity, and inclusion and determine whether the evidence can be generalized to underrepresented, disproportionately affected, or understudied populations. More detailed information (e.g., disaggregated data by age group such as <65, 65-74, 75-84, and >=85 years) will be important considering the racial and ethnic disparities in the prevalence of AD and other dementias among the subpopulations³ and increasing diversity among older people.⁴

We believe that it would be helpful to acknowledge the relatively small percentage of people in the older subgroup of older adults with AD who are expected to be candidates for treatment. Older people with cognitive impairment, including early-stage dementia, often manage a number of concurrent chronic medical conditions⁵ and beyond exclusion by age, older adults are often excluded in clinical trials due to their comorbid conditions.⁶ it is essential to understand how the clinical trials for the beta-amyloid antibodies managed patients with comorbid conditions as it impacts the cost and outcome estimates.

Additionally, the populations section of the draft scope indicates that evidence of AD pathology can be determined by "amyloid positivity **OR** pathological tau." However, tau is abnormal in neurodegenerative disease other than AD.⁷ The AGS strongly urges ensuring that amyloid accumulation is a required criterion, and not tau alone.⁸

Interventions

Further delineation of the non-pharmacologic and non-disease-modifying pharmacologic interventions that constitute supportive care would be helpful for a more in-depth understanding of the interventions' impact and effectiveness. The AGS also recommends clarification around the use of medications to treat symptoms (e.g., acetylcholinesterase inhibitors, memantine) – whether the prescription would change and the likelihood of medication suspension or nonuse.

Comparators

The AGS encourages the consideration of prescribed medications to treat symptoms of AD in the comparisons of anti-beta-amyloid therapies and supportive care to supportive care alone.

Outcomes

In addition to the outcomes of interest described in the draft scope, the AGS encourages the inclusion of other adverse events that occurred during treatment that are not necessarily related to amyloid-related imaging abnormalities (ARIA) or death. We believe that the data collected in the clinical trials on standardized adverse events—where the cause of the event is typically not hypothesized—should be included in the assessment.

The AGS supports the addition of a measure on the burden of prescribing, approving, and receiving the beta-amyloid antibody treatments for patients/caregivers, prescribers, and insurers. For patients/caregivers, it may be beneficial to know the number of visits and phone calls as well as time spent by patients and/or caregivers to qualify and arrange to receive each dose in addition to the supplementary appointments for monitoring, labs, and scans. The time spent to submit

information to meet prior authorization requirements for approval and appeals, referring patients to centers for the drug administration, monitoring efficacy, and arranging review and follow-up for labs and scans can be significant for prescribers and similarly for Medicare and other insurers (e.g., reviewing prioritization requests and appeals, payment processing). We hope to understand whether these tasks add to or reduce similar burden of caring for untreated patients.

Some additional measures that may be of interest include a caregiver assessment; the time spent outside of the medical care system; measures that patients and caregivers thought were missing from clinical trials; and additional geriatric patient-specific measures. The AGS believes that the outcomes should be aligned with what matters most to persons living with dementia and their caregivers and families. Geriatrics health professionals focus on the 5Ms of geriatrics: Multimorbidity, What Matters, Medication, Mentation (cognitive function), and Mobility (physical function).⁹ Multimorbidity describes the older person who has more complex needs often due to multiple chronic conditions, frailty, and/or complex psychosocial needs. What Matters, Medication, Mentation and form the basis for the age-friendly health systems framework that is focused on ensuring that all older people have access to this type of coordinated care, while also making sure personal needs, values, and preferences are at the heart of that care.¹⁰ Cognitive function and physical function are especially important to older adults as reflected in conceptual models for what matters most to older adults such as the 5Ms.¹¹

Timing

We agree that studies of any duration should be considered when evaluating evidence on intervention effectiveness and evidence of harms. Additional considerations include whether studies were prematurely terminated and the factors that lead to that termination.

Settings

The AGS believes that the treatment setting should be inclusive of treatment team capacity. In addition to the site of care, we recommend exploring whether the treatment setting facilitates appropriate monitoring for any adverse events as well as cognitive function to assist in determining whether the patient is benefitting from treatment, and if not, to help decide whether to terminate treatment using shared decision-making. Ideally the patient's care team would be interprofessional, inclusive of cognitive specialists and clinicians with geriatrics expertise along with a social worker, registered nurse, and pharmacist.

Thank you for taking the time to review our feedback and recommendations. For additional information or if you have any questions, please do not hesitate to contact, Anna Kim at <u>akim@americangeriatrics.org</u>.

Sincerely,

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Peter Hollmann, MD President

Monuz E. Andajez

Nancy E. Lundebjerg, MPA Chief Executive Officer

AGS Comments on ICER's Draft Scoping Document on Beta-Amyloid Antibodies for Early Alzheimer's Disease Page 3

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⁹ Adapted by the American Geriatrics Society (AGS) with permission from "The public launch of the Geriatric 5Ms" [on-line] by F. Molnar and available from the Canadian Geriatrics Society (CGS) at https://canadiangeriatrics.ca/2017/04/update-the-public-launch-of-the-geriatric-5ms/.

alzheimer's $\ref{eq:station}^*$

Institute for Clinical and Economic Review (ICER) Two Liberty Square Ninth Floor Boston, Massachusetts 02109

January 19, 2022

To Whom It May Concern,

On behalf of the Alzheimer's Association, all those living with Alzheimer's disease, their caregivers, and their families, we appreciate the opportunity to comment on ICER's Draft Scoping Document on Beta-Amyloid Antibodies for Early Alzheimer's Disease. Our comments are provided according to the headings in the draft document.

Background

We note ICER's description of aducanumab as "the first *potential* disease modifying treatment for patients with AD." [Emphasis added.] We remind ICER that the Food and Drug Administration determined that aducanumab consistently and significantly reduced the level of amyloid plaques—the defining characteristic of the disease—and that there was a reduction in clinical decline in individuals, providing evidence that aducanumab can slow the progression of Alzheimer's disease.

Stakeholder Input

The document states that ICER "...encourages comments to refine our understanding of the clinical effectiveness and value of preventive treatments." However, the therapies at the center of this analysis are not being proposed as preventative therapies.

ICER also includes in the document that many patients and their families do not receive adequate counseling about how to navigate the disease at the time of diagnosis and that at the time of diagnosis, individuals should receive "comprehensive care planning . . ., linkage to social services, management of comorbidities, information on clinical trials, and discussions about end-of-life care." We note that in addition to inadequate counseling, many people with Alzheimer's do not receive a diagnosis at all, which is a primary barrier to care and treatments. We also encourage ICER to add "treatment options" to the list of services individuals and families should receive at diagnosis given the newly-available therapy and those in the pipeline.

The Alzheimer's Association agrees with ICER's statement that the main goal of patients and caregivers is to prolong the time individuals remain independent. We believe this is also a societal goal given the impact of Alzheimer's disease on our country.

We also agree with the need for the development of better measures of patient-important outcomes, and we believe that to truly understand the impact of a therapy, longitudinal measurement of such outcomes is required. This can be achieved through coordinated efforts to develop and maintain a registry, such as the National Treatment and Diagnostic Alzheimer's Registry that the Association is launching with the American College of Radiology, the American Society of Neuroradiology, the Brown University School of Public Health, and other stakeholders.

The document states that "Although some [clinicians] are cautiously optimistic about antiamyloid therapies, because there have been multiple purported disease-modifying drugs that have previously failed during the clinical trial phase, they would like clearer evidence demonstrating the efficacy of such therapies on clinical outcomes." We ask that ICER clarify whether it is referring to anti-amyloid candidates or other therapies as well. It goes on to assert that "...they feel that many of the outcomes used in clinical trials do not reflect the full spectrum of AD symptoms and have the potential of being biased based on ceiling effects or the perceived expectations of the observer (expectancy bias)." The Alzheimer's Association does not believe that anyone expects that trials would reflect the full spectrum of AD symptoms. Furthermore, expectancy bias is controlled by using a double-blind experimental design.

Outcomes

The Alzheimer's Association appreciates ICER's inclusion of those outcomes most important to persons living with Alzheimer's and caregivers, as well as caregiver impact outcomes. We hope that all of these outcomes are factored into ICER's economic analysis in a more robust way than previous analyses. With regard to including neurogranin, the Alzheimer's Association is unaware of any neurogranin data related to aducanumab, donanemab, or lecanamab. If those data exist, we support their inclusion, but if they do not, neurogranin should not be included as an outcome in this analysis.

Potential Other Benefits and Contextual Considerations

With regard to "Potential Other Benefit or Disadvantage," ICER intends to consider "Patients' ability to manage and sustain treatment given the complexity of regimen." Given the person with dementia-caregiver dyad, care partners should be included when considering the ability to manage a regimen.

Scope of Comparative Value Analyses

As ICER may reevaluate the economic impact of aducanumab, we note Biogen/Eisai's recent announcement of a reduction in the price of the drug.

ICER intends to include caregiver impacts (e.g., quality of life, lost productivity) in its economic analysis. We respectfully request that ICER provide specific examples of the data it would consider. We also request, as noted above, that the economic analysis fully take into account all outcomes, including those most important to individuals and caregivers, such as the ability to communicate and emotional wellbeing.

When building its economic model, we urge ICER to consciously consider the MRI schedule, as different clinicians are using MRI at different frequencies. How often MRIs are used will affect the model and projections from it.

Identification of Low-Value Services

While we do not suggest any services that could be reduced, eliminated, or made more efficient at this time, we urge ICER to consider that changes in positron emission tomography (PET) coverage and approval and coverage of cerebrospinal fluid (CSF) or blood biomarker diagnostics could change mechanisms of care, efficiencies, and cost in the future.

Thank you for the opportunity to comment. Please do not hesitate to contact Matthew Baumgart, Vice President of Health Policy at <u>mbaumgart@alz.org</u> or 646.849.9978 if we can be of additional assistance.

Sincerely,

KJoanne Pike

Joanne Pike, DrPH President



Eisai welcomes the opportunity to comment on ICER's *Draft Background and Scoping Document for Beta-Amyloid Antibodies for Early Alzheimer's Disease*. Eisai considers this document its response to an unsolicited request by ICER for scientific information. Few diseases steal as much from patients and caregivers as Alzheimer's Disease (AD). The 7th leading cause of death in the U.S.,¹ AD devastates the lives and finances of patients and their families and stands as a formidable public health threat as society continues to age. Afflicting approximately 6 million adults, 1 in 6 patients over the age of 80 and older suffer from Alzheimer's dementia.^{2,3} While over 200 AD drug candidates have failed over the last two decades,⁴ anti-amyloid beta (Aβ) antibodies show great promise for AD patients. This is due to great strides in AD drug innovation, including better trial design that includes only patients who have biomarkers for AD at an early stage of disease; and a better understanding of how amyloid, specifically the accumulation of Aβ protofibrils, contributes to AD and worsening brain function.^{5,6}

Eisai's believes that its investigational agent, lecanemab, is unique among anti-A β antibodies and shows promise for early AD patients.⁷ Lecanemab differs from other anti-amyloid therapies in its capacity to preferably target soluble A β protofibrils. Among the most toxic A β forms, these protofibrils are reported to be a major cause of AD and the associated loss of cognition.^{8,9} It is increasingly recognized that targeting one soluble species of A β also reduces other forms of A β .¹⁰ While other anti-amyloid therapies mainly bind to larger insoluble fibrils, lecanemab's targeting of these soluble protofibrils and to a lesser extent, amyloid plaques, result in a high degree of A β plaque clearance in trials, the extent of which correlates with slowing of clinical decline.^{11,12,13} The results of the phase 2b proof-of-concept trial supported lecanemab's breakthrough therapy designation by the FDA.¹⁴

In trials, lecanemab was well tolerated while demonstrating a consistent dose response. While no headto-head data exist versus active compounds, review of clinical trial data showed that lecanemab has lower amyloid-related imaging abnormalities-edema (ARIA-E) in trials than other anti-A β therapies. This allows for the initiation of treatment at the therapeutic dose without titration. Less than 10% of Study 201's (BAN2401-G000-201) total population treated with 10 mg/kg biweekly experienced ARIA-E, and less than 2% experienced symptomatic ARIA-E.^{15,16}

We recognize ICER's role in navigating the efficacy and affordability of new treatments and offer the following recommendations to guide this effort.

1. Efficacy: Apply the full treatment effect of lecanemab in ICER's cost-effectiveness modeling.

We recommend ICER apply data from Study 201 and the 201 open-label extension, and avoid any efficacy assumptions where known trial data exist.¹⁷ Lecanemab reduced brain Aβ, slowed clinical decline, and displayed a consistent dose response in the 18-month Study 201, where the primary clinical outcome was measured using the AD Composite Score (ADCOMS).¹⁸ Developed by Eisai, ADCOMS combines the most responsive items from AD diagnostic tools (both cognitive and functional scales) and was implemented in Study 201 due to its superior sensitivity to clinical decline – versus other scales.^{19,20} As shown in Figure 1 in the Appendix, at 18 months, lecanemab resulted in 30% less clinical decline on ADCOMS, 26% less decline on Clinical Dementia Rating Scale Sum of Boxes (CDR-SB), 47% less decline on Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog)14, and as shown in Figure 2, displayed a dose-dependent reduction in brain amyloid positron emission tomography (PET).²¹ It should also be noted that the 12-month analysis was incorporated to expedite progression to phase III in the event of early success based on early



"super-superiority" over placebo (*i.e.*, >25% slowing of clinical decline)²² with an overall double-blind study period of 18-months.²³

Lecanemab's Phase 2b results show a correlation in slower clinical decline with the reduction in amyloid and corresponding changes in amyloid and tau biomarkers. Data presented at the 2021 14th Clinical Trials on Alzheimer's Disease (CTAD) conference^{24,25} showed that lecanemab reduced brain amyloid as early as three months of treatment in the open label extension (OLE). Moreover, after 18-months of treatment at the highest dose of 10 mg/kg IV biweekly, over 80% of the early AD patients became amyloid negative by visual read on a PET scan in both the double-blind treatment phase, and in newly treated patients in the OLE.^{26,27} The Phase 2b study of 856 AD patients presented consistent clinical efficacy results across various endpoints, including treatment effect after 18-months of treatment with lecanemab (10 mg/kg biweekly) for all three clinical scales; ADCOMS, CDR-SB, and ADAS-Cog.²⁸

2. Treatment Length: Model treatment length only until patients transition to moderate AD.

Eisai recommends that ICER's model assumes that patients who benefit from lecanemab stay on treatment until they progress to the moderate stage.²⁹ Once reaching the moderate stage, patients should stop treatment. Lecanemab's efficacy and safety have not been clinically evaluated by Eisai beyond the mild stage, and ICER should only model indicated populations (MCI due to AD and Mild AD) to avoid unnecessary costs to the health system.

Patients require treatment beyond 18 months to avoid progression. The clinical and biomarker treatment effect of lecanemab versus placebo at the end of the core treatment was maintained while off-treatment during the gap period up to the beginning of the OLE in early AD patients, although overall rate of progression (slope) in the gap period was similar in the core treated and placebo groups for amyloid PET SUVr and ADCOMS. But as shown in Figure 3 of the Appendix, discontinuation of treatment during the gap period resulted in a gradual decrease in the plasma $A\beta42/40$ ratio and increase in plasma p-tau181, which may be an early indicator of re-accumulation of soluble aggregated $A\beta$ species and downstream tau pathology. The results of this "delayed stop design" are consistent with a disease modifying effect, and the potential for further benefit with maintenance treatment even after amyloid is cleared. Eisai is exploring less frequent dosing regimens after amyloid clearance in order to maintain plasma biomarker levels.

3. Discontinuation: Incorporate discontinuation rates from the clinical trials.

We recommend ICER apply Study 201's 25% discontinuation rate (10mg/kg bi-weekly: 13.7% (22/161) from AEs, 11.2% (18/161) from subject choice).^{30,31} In Study 201, 35.6% (217 subjects) in the BAN2401 treatment groups discontinued compared to 23.3% in the placebo (57 subjects). Discontinuation was higher in the BAN2401 10 mg/kg monthly and biweekly groups, (92 [36.4%] and 71 [44.1%] subjects, respectively). Additionally, twenty-five subjects who were ApoE4 carriers and on 10 mg/kg biweekly for less than 6 months were discontinued in accordance with Regulatory Authority (VHP) request. We believe that this implementation was the primary driver for the observed higher discontinuation rate due to "Other" in ApoE4 carriers (25 [52.1%] subjects), compared to ApoE4 non-carriers (6 [5.3%] subjects). It is therefore reasonable to consider a discontinuation rate of ~25% (AE (22) + subject choice (18) = 40/161 24.8%). This adjusted rate is comparably lower because of the ARIA-E events (<10% incidence at 10mg/kg biweekly)– the primary cause of discontinuation – and an even lower occurrence of symptomatic ARIA-E (<2%).^{32,33}



Lecanemab does not require titration, so patients receive the effective dose from treatment initiation. Other amyloid clearing treatments that require a titration period may result in more patients staying on treatment as the dosage gradually increases, with patients discontinuing treatment later as they reach the full dosage, and adverse effects may become more apparent. We believe that lecanemab's single dose regimen will shorten the span of discontinuations to within the first three months of initiation,³⁴ creating significant cost savings, and optimizing resource use. Also, the lack of dose titration may explain the difference in plaque clearance between lecanemab (>81% at 18-months) and other selected anti-amyloid therapies (for example, 67.8% at 18-months for another anti-amyloid therapy).^{35,36}

4. Caregiver Burden: Capture caregiver burden by adding new sources of caregiver costs and quality of life (QoL) impact.

AD caregivers suffer from heightened physical and mental health issues, watching their loved ones deteriorate while becoming removed from everyday life.³⁷ The Clarity AD trial^{38,39} has enrolled 1,795 patients, and is expected to provide direct evidence on lecanemab's outcomes for caregivers, including caregiver QoL. Lecanemab's consistent reduction of clinical decline in its early stages could prolong a patient's independence. Greater independence would reduce the hours of unpaid weekly care, lessen the burden of annual out-of-pocket costs borne by caregivers, and potentially delay the need for professional long-term care, saving families up to 40% of the over \$100,000 yearly costs.^{40,41,42} Diminishing AD progression in the early stages also provides more time for patients to autonomously make decisions about their future care, reducing uncertainty and stress for their families. However, the most precious benefit for a caregiver is every extra moment – be it a day, month, or year – that is enjoyed with a loved one before their memory is entirely, irreparably lost.

The burden of caregiving disproportionately impacts women, African Americans, and Hispanic populations, making AD a potent aggravator of existing disparities.⁴³ Eisai is committed to the mission of contributing meaningful innovations that will improve the lives of patients and caregivers and address this unmet public health crisis. As part of our commitment, Eisai and our partners are working to recruit more underrepresented ethnic groups than any other anti-amyloid trial to date.^{44,45,46}

5. Willingness-to-pay (WTP) Thresholds: Consider WTP thresholds that account for disease severity and public health impact – this new approach would lead to increased WTP thresholds.

ICER should adopt an economic assessment perspective that is more consistent with U.S. law (*i.e.*, the Affordable Care Act and related policy concerns on the inherent bias in traditional cost-effectiveness (C/E) modeling). If traditional C/E analysis continues to be used, necessary caution needs to be taken to address these concerns as it may lead to gross under-representation of healthcare value for patient populations with severe health conditions. Lakdawalla *et al.* have proposed a more equitable, Risk-Adjusted-Cost-Effectiveness (GRACE)⁴⁷ approach that assigns higher WTP thresholds (up to \$600,000) for more severe diseases like AD.

Summary

Conscientious consideration for patient preferences should sit at the heart of ICER's assessment. For such a devastating diagnosis, it would be unacceptable to devalue any therapy offering a chance of improvement. With its potential to slow cognitive decline, lecanemab provides hope for AD patients and their caregivers in facing this elusive stealer of minds.



Appendix



Figure 1. Effect of top 2 doses of lecanemab on clinical outcomes

Primary outcome required: 80% probability of >25% slowing at 12-months to rapidly advance to Phase 3 was not met (64%). At 18-

ssment Scale-cognitive subsc elona, Spain. October 25, 2018



Figure 2. Amyloid clearance (PET SUVr) correlates with clinical efficacy **Group level data**

Adjusted mean was based on a mixed effects model with repeated measures (MMRM). The MMRM model included baseline as a covariate, with treatment group, visit, region, randomization stratification variables (clinical stage, concurrent AD medication, APOE4 status), and treatment group-by-visit interaction as fixed effects. Data shown are for subjects enrolled in the PET sub-study at with data at 18 months (N=277). Presented at the Clinical Trials on Alzheimer's Disease (CTAD) Conference October 24-27, 2018

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Figure 3: Stopping lecanemab is associated with an increase in amyloid-beta and associated clinical decline

Lecanemab^{*1} (BAN2401): Anti-Aβ Protofibril Antibody Eisai New era of plasma biomarker to potentially track disease progression and treatment effect

Plasma Aβ42/40 ratio demonstrates relationship to amyloid PET^{*2} and disease progression^{*3}

- Increase in plasma Aβ42/40 ratio during lecanemab treatment correlated with PET SUVr^{*4} and clinical outcomes during lecanemab treatment phases in Study 201 Core and Study 201-OLE*5 while losing correlation in untreated Gap period
- Discontinuing treatment allows plasma Aβ42/40 ratio to start decreasing again, which is an early indicator of brain Aβ plaque accumulation and is associated with clinical decline observed after treatment discontinuation. These findings suggest that continued treatment may be beneficial for patients while still in the Early AD Stage



Lecanemab^{*1} (BAN2401): Anti-Aß Protofibril Antibody Fast, deep and sustained clearance of Aß plagues and acceptable tolerability were suggested

- No titration is required, allowing patients to receive the highest dose (10mg/kg biweekly) from the beginning of the treatment
- Aβ plaque reduction was observed at 3 months in Study 201-OLE*2 (fast clearance)
- In both Study 201 Core and Study 201-OLE, brain amyloid was reduced to negative levels in ≥80% subjects*3 (deep clearance)
- Aß plaque level differences from subjects who received placebo in Study 201 Core were maintained during Gap period



Favorable safety profile in the highest dose

Eisai

- The incidence of ARIA-E^{*5} was 9.9% ≻ for the group at the highest treatment dose (10mg/kg biweekly) in Study 201 Core
 - The incidence of ARIA-E was 0.8% in placebo arm and not more than 10% in any of the treatment arms in Study 201 Core
 - Approximately 60% of ARIA-E occurred within first 3 months of treatment and MRI findings were typically resolved within 4-12 weeks
- For subjects who received 10mg/kg biweekly during 201-OLE after receiving placebo in 201 Core, the incidence of ARIA-E was 8.9%, consistent with the rate observed during the 201 Core study



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²⁰ Op. cit. Wang et al. 2016. Link 3

²¹ Op. cit. Swanson et al. 2021. Link

²² Op. cit. AlzForum. 2021. Link

²³ Op. cit. Swanson et al. 2021. Link

²⁴ Op. cit. AlzForum. 2021. Link

²⁵ BioArctic. New data on lecanemab presented at the CTAD Alzheimer conference. Cision PR Newswire. 15 Nov 2021 [cited on 06 Jan 2022]. Link

²⁶ Op. cit. Swanson et al. 2021. Link

²⁷ Op. cit. AlzForum. 2021. Link

²⁸ Op. cit. BioArctic. 2021. Link

²⁹ In the last AD assessment, ICER applied treatment until progression to severe AD as its base case even though Aduhelm® trials did not evaluate efficacy and safety in patients with moderate or severe AD, nor was this reflected in the approved FDA label.

- ³⁰ Op. cit. Swanson et al. 2021. Link
- ³¹ *Op. cit.* Mintun *et al.* 2021. Link
- ³² Op. cit. Swanson et al. 2021. Link
- ³³ Op. cit. BioArctic. 2021. Link
- ³⁴ Op. cit. Swanson et al. 2021. Link
- ³⁵ *Op. cit.* Swanson *et al.* 2021. Link
- ³⁶ *Op. cit.* Mintun *et al.* 2021. Link



³⁷ Op. cit. Alzheimer's Association. 2021. Pg. 13. Link

³⁸ ClinicalTrials.gov. A study to confirm safety and efficacy of lecanemab in participants with Early Alzheimer's Disease (Clarity AD). 19 Oct 2021 [cited on 10 Jan 2022]. Link

- ³⁹ Eisai. Lecanemab Phase 3 Clarity AD Clinical Trial Completed Enrollment. Eisai. 20 April 2021 [cited on 10 Jan 2022]. Link
- ⁴⁰ Op. cit. Alzheimer's Association. 2021. Pg. 41. Link
- ⁴¹ Op. cit. Alzheimer's Association. 2021. Pg. 60. Link

⁴² National Academy of Social Insurance. Long-term services and supports. Cited 2022 Jan 5. Link

⁴³ Op. cit. Alzheimer's Association. 2021. Pg. 24-25. Link

⁴⁴ 2021 AAIC Annual Meeting [Poster #54331]. Baseline Characteristics for CLARITY-AD: A phase 3 placebo-controlled, double-blind, parallel-group, 18-month study evaluating lecanemab (Ban2401) in Early Alzheimer's Disease. BioArctic. Jan 2021 [cited on 06 Jan 2022]. Link

⁴⁵ AlzForum. Aduhelm. AlzForum. 22 Dec 2021 [cited on 06 Jan 2022]. Link

⁴⁶ Op. cit. Mintun et al. 2021. Link

⁴⁷ Lakdawalla DN, Phelps CE. Generalized Risk-Adjusted Cost-Effectiveness (GRACE): Ensuring Patient-Centered Outcomes in Healthcare Decision Making. ISPOR. 2021;7(2). Link

Comments on ICER Scoping Document Howard Fillit, MD January 8, 2022

Generally, this is well written, comprehensive, and addresses key points in Alzheimer's disease monoclonal antibody anti-amyloid drug development.

On Page 2, end of third paragraph, there is a statement that current drugs on the market "...have been shown to be effective in stabilizing cognitive and functional symptoms of the disease." I do not agree with this statement. Current treatments, including cholinesterase inhibitors and memantine, do not "stabilize" symptoms. For most patients, there is simply a very modest, perhaps 6 months delay in the progression of symptoms, which then follow a rate of progression that is parallel to the placebo rate of progression, without a change in slope. The effects seen in clinical practice by patients and physicians are generally considered not clinically meaningful. This further emphasizes the current need for effective therapies.

On page 3, end of paragraph 3, there is a statement that "ICER looks forward to...refine our understanding of the clinical effectiveness and value of preventive treatments." The treatments that are the focus of the scoping documents are generally not considered preventive, unless ICER considers slowing the progression of MCI to mild dementia a form of "secondary prevention."

On page 3, last paragraph, the document states "The main goal...is to prolong the time the patients remain independent..." This is not strictly accurate. Patients with mild dementia are generally dependent in most instrumental activities of daily living (IADL) and often require supervision with some basic activities of daily living. Patients with mild cognitive impairment have been shown to be impaired in some IADLs. Therefore, the accurate representation of the therapeutic goals for functional impairment should read something along the lines of "slowing the rate of functional decline." Similarly, the statement "...are eager for treatments that will help the patient remain independent..." are unrealistic and inaccurate, and should be revised to state that patients are eager to maintain or improve their current functional impairment, and achieve the highest level of independent function possible."

Under Populations (page 5), I believe evidence of beta-amyloid positivity is unique to Alzheimer's disease, while elevations in tau are not specific but add to the diagnostic validity. Therefore, I recommend changing "...evidence of AD pathology (e.g. amyloid positivity or pathological tau" and "baseline levels of AD pathology (e.g. beta-amyloid or phospho-tau levels)" to "evidence of AD pathology (eg. beta-amyloid positivity, with positivity on pathologic species of phospho-tau adding to the diagnostic certainty.")

Under Outcomes, for Patient-important Outcomes, for ability to maintain independence and autonomy, I suggest changing to "improvement or stabilization of functional impairment." for cognitive function I suggest adding the MOCA since this is widely used in clinical practice, and especially in patients with MCI. I also suggest some the influence of some measures of co-

morbidity, such as microvascular disease in the brain on MRI, and the presence of diabetes and hypertension, as covariates in the analyses. Most patients in the community (~50%) have "mixed dementia" with AD and vascular components, making this a clinical relevant population for the analysis.

Under Other Outcomes, I suggest adding plasma levels of beta-amyloid and pathological species of tau, since these are currently being incorporated into clinical trials and show great promise in decreasing the cost of screening, diagnosis and therapeutic monitoring in both clinical trials and in clinical care. I am not sure why neurogranin was included, but other exploratory markers could also be included, such as plasma neurofilament light and GFAP.

The economic modeling proposed is excellent. I hope it is realistic. Demonstrating costeffectiveness from clinical trial data in Alzheimer's is fraught with difficulty. The event rates for critical cost events such as hospitalization are low, and often do not occur during the time frame of the clinical trial, especially since the patients in clinical receive better care than those in the community who are not in trials. Therefore, expectations of success in demonstrating cost-effectiveness should be limited. If possible, in order to capture event rates that may occur as a result of treatment but beyond the time frame of the trial, I suggest attempting to obtain Medicare claims data on patients (via ResDac) to obtain a more accurate and clinically relevant health care system perspective over a longer period of time (for the 5 year time horizon that is suggested in the document, page 8, last paragraph). (See Fillit, et al, J Nutr Health Aging 2010 Oct;14(8):640-7)

For caregiver outcomes, we have shown that there are differences in caregiver impacts as they relate to caregiver burden and caregiver time that may be affected by treatment. While burden (level of care for example) may decrease, caregiver time may not. (see Fillit, et al Int Psychogeriatr 2000 Sep;12(3):389-401).

Finally, for Identification of Low-value services, cognitive assessments (especially for MCI patients) that may involve neuropsychological testing could be greatly reduced by digital technology being developed for cognitive and even functional assessments. These technologies are being assessed in clinical trials, and tested in community based clinical care populations. Similarly, blood plasma tests are already being deployed in both clinical trials and in clinical practice and will have a significant impact on screening, diagnostic certainty, early diagnosis, and therapeutic monitoring. Digital technologies may also improve care management by the use of algorithms and more efficient methods to monitor the safety and functional needs of patients and their caregivers.

Howard Fillit, MD

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Eli Lilly and Company Lilly Corporate Center Indianapolis, Indiana 46285 U.S.A. www.lilly.com

January 19, 2022

RE: Lilly's Written Response to ICER's Draft Scoping Document

Eli Lilly and Company ("Lilly") appreciates the opportunity to provide feedback on the Institute for Clinical and Economic Review's (ICER's) draft scoping document for the assessment of beta-amyloid antibodies for early Alzheimer's disease (AD). Below are several recommendations ICER should incorporate in its review.

Patients and caregivers urgently need new disease-modifying therapies for AD

AD's fatal impact on patients, huge burden on caregivers, and high healthcare system costs, which ICER noted in its draft scoping document, demonstrate why new disease-modifying therapies are urgently needed. ICER's draft scoping document appropriately describes AD as being defined by pathological changes to proteins in the brain: the accumulation of beta-amyloid plaques and neurofibrillary tangles of phosphorylated tau. Accumulation of beta-amyloid plaque is hypothesized to trigger the spread of tau, which is correlated with clinical decline in cognition and function (Busche et al., 2020). Recent clinical trials of amyloid-clearing agents have demonstrated significant lowering of beta-amyloid plaque levels along with slowing of clinical progression or lower tau levels, or both. (Swanson et al., CTAD, 2021; Hansson et al., 2021; Mintun et al., AAIC, 2021). Such downstream impacts provide strong evidence that removing amyloid plaques can potentially modify both clinical disease progression and the underlying disease pathology. In the Phase 2 TRAILBLAZER-ALZ clinical trial, donanemab demonstrated rapid clearance of amyloid plaques and a significant slowing of disease progression (Mintun et al. 2021). Lilly is currently conducting TRAILBLAZER-ALZ2, a Phase 3, double-blind, placebo-controlled study to verify the safety and efficacy of donanemab in participants with early symptomatic AD. Topline results are expected in the first half of 2023 (Lilly Alzheimer's Clinical Trials, 2021).

ICER should use biomarkers to predict long-term benefits beyond treatment duration

In its previous review of aducanumab, ICER assumed the benefits of treatment would end when patients entered the moderate stage of AD, but that treatment would continue until patients entered the severe stage (Lin et al., 2021). Instead, ICER should base assumptions regarding long-term benefit on each molecule's biomarker data. Good practice in economic evaluations is to choose a time horizon long enough to capture all relevant costs and benefits, then extrapolate data to match that timeframe (Sanders et al., 2016; Barbarino et al., 2021). Biomarker data from TRAILBLAZER-ALZ suggest the duration of benefit from donanemab extends beyond the duration of treatment. TRAILBLAZER-ALZ patients who reached amyloid clearance at six months were switched from donanemab to placebo in a blinded manner. Treatment was discontinued because patients no longer had imaging evidence of the presence of amyloid plaque. These patients' amyloid levels were measured for the remaining 12 months of the trial. During that time, those patients re-accumulated amyloid at a very slow rate. Also, patients who stopped donanemab treatment at six months had plasma P-tau217 levels remain at reduced levels for the subsequent 12 months-demonstrating little difference from patients who continued to receive donanemab for 18 months (Sims et al., CTAD, 2021). The combined and persistent reduction in both amyloid and P-tau217 is evidence that donanemab modified the disease pathology, therefore Lilly believes disease progression in donanemab patients could continue to be slowed for years beyond donanemab's duration of treatment. Biological modelling predicts it would take 3-4 years for patients to re-accumulate enough amyloid to be detectable by PET scans and more than 14 years to reach their pre-treatment levels (Sims et al., AAIC, 2021). In its cost-effectiveness modelling, ICER should incorporate this range of treatment benefit duration.

ICER should incorporate diagnostics to identify patients and discontinue donanemab treatment

Across the anti-amyloid class, we recommend that ICER assume the use of diagnostics that identify evidence of amyloid pathology consistent with AD, which can enable appropriate determination of patients for these therapies. Furthermore, we recommend ICER incorporate in its review of donanemab the use of positron emission tomography (PET) scans to determine when patients have reached amyloid clearance and should stop treatment, resulting in a limited-dosing regimen rather than a chronically administered therapy. Donanemab is unique among amyloid-lowering antibodies in that it binds only to deposited amyloid plaques. Lilly believes that once amyloid clearance is reached, it is unnecessary to continue to treat patients with donanemab. In TRAILBLAZER-ALZ, 40% of patients reached amyloid clearance by six months, 60% by 12 months and 68% by 18 months. An independent cost-effectiveness analysis previously assumed patients taking donanemab would end treatment after 6, 12 or 18 months (Ross et al., 2021). Incorporating the use of diagnostics will significantly alter the cost-effectiveness and budget impact assessment of donanemab. ICER's review of aducanumab did not include diagnostics for identifying appropriate patients or treatment monitoring (Lin et al., 2021). However, with the availability of new AD therapies, utilization of such diagnostics will likely increase.

ICER should wait to analyze subpopulations

Given the critical role of abnormal accumulation of brain proteins in the appropriate identification and treatment of AD (Rabinovici et al. 2019), we agree with ICER's focus on patients with mild cognitive impairment (MCI) or mild dementia due to AD, with evidence of AD neuropathology. ICER's proposed population also aligns with the most recent clinical trials for donanemab, lecanemab and aducanumab. However, we encourage ICER *not* to undertake analyses for the subpopulations listed in its draft scoping document at this time. Currently available clinical trial data for donanemab and other amyloid-lowering treatments are not powered to support clinical or economic analyses of subpopulations, which could lead ICER to make preliminary and potentially inaccurate conclusions. Phase 3 trial readouts are anticipated within the next 18 months for donanemab and lecanemab. It would be more appropriate to conduct subgroup analyses when those data are available.

Lilly supports ICER's planned approach to analyzing adverse events

Lilly agrees that ICER's assessment should focus on symptomatic amyloid-related imaging abnormalities (ARIA), a potentially serious class-related side effect of amyloid-lowering antibodies. It appears ARIA occurred most frequently in patients, such as APOE4 carriers, who also saw the most efficacy from these treatments (Sims et al, CTAD, 2021). Therefore, safety should be considered alongside a treatment's overall benefit. We believe TRAILBLAZER-ALZ demonstrates donanemab's strong net health benefit. Most cases of ARIA in TRAILBLAZER-ALZ were asymptomatic and occurred during the first 12 weeks of treatment. Overall, 6.1% of participants taking donanemab experienced symptomatic ARIA-edema/effusion (ARIA-E). With or without symptoms, seven donanemab patients (5.3%) discontinued treatment and two donanemab patients (1.5%) discontinued the trial due to ARIA-E. Notably, discontinuations due to ARIA were driven by strict trial protocol criteria and may be different in real world practice. Overall in TRAILBLAZER-ALZ, no significant difference was found between the donanemab group and the placebo group in the incidence of death or participants reporting at least one serious adverse event (AE). Treatment discontinuations due to AEs were 30.5% in the donanemab group versus 7.2% for placebo.

Each molecule should be compared to best supportive care separately using its studied primary endpoint

ICER's typical practice of making indirect comparisons across clinical trials via a network meta-analysis (NMA) would be inappropriate in this assessment. Each anti-amyloid therapy has been studied in different patient populations, with differing levels of cognitive decline and AD neuropathology at baseline. Also, there have been no head-to-head trials in this class. Due to these differences, the three assumptions required for an NMA—similarity, consistency, and lack of heterogeneity—have not been met (Cipriani et al., 2013). Furthermore, the clinical trial data for these treatments are insufficient for the purpose of indirect comparisons. By relying on a small number of Phase 1 and Phase 2 studies, an NMA would be underpowered to detect

differences across trials in the clinical endpoints that are available. In general, an indirect comparison would require three or four trials per treatment to have the equivalent power of a head-to-head study (Glenny et al., 2005; Thorlund et al., 2012). Instead of an NMA, each molecule should be compared against best supportive care using the primary endpoint from its most recently completed clinical trial. It has been common to choose CDR-SB as an endpoint, however, low inter-rater agreement on the CDR-SB in populations with mild AD dementia has been reported (Burke et al., 1988; McCulla et al., 1989; Morris et al., 1997; Rockwood et al., 2000; Tractenberg et al., 2001). There is significant interest in developing composites that may be more sensitive to detect disease progression in the early AD population (Schneider et al., 2020). The Integrated Alzheimer's Disease Rating Scale (iADRS) is one alternative shown to be a more sensitive and reliable measure across identically designed clinical trials than the CDR-SB (Doody et al., 2014; Wessels et al., 2018; Haeberlein et al., 2021). Therefore, to improve the sensitivity and reliability of its clinical assessment, we recommend ICER evaluate donanemab using the iADRS rather than a secondary endpoint.

Lilly recommends more direct incorporation of societal factors and a broader array of outcomes

All AD therapies should aim to achieve the "patient-important outcomes" included in ICER's scoping document; however, many of these measures are long-term in nature, meaning evidential data is either immature or unavailable at this time. There remains work to do to determine and validate appropriate methods for measuring and analyzing these outcomes. What can be improved immediately is more direct incorporation of societal factors. It is widely recognized that the healthcare system perspective adopted by ICER as its base case for cost-effectiveness analysis, by focusing on direct medical costs, fails to account for much of the burden of AD (Lin and Neumann, 2021). This includes elevated severity, health inequities, full costs of institutionalization, and family impacts. In its previous assessment of aducanumab, ICER attempted to correct for such limitations by conducting a co-base case from a societal perspective; however, ICER's approach yielded a result almost no different from the healthcare perspective. Therefore, instead of considering "acuity of need" and "severity of the condition" as merely contextual factors, ICER should consider these factors explicitly in its cost-effectiveness thresholds, in line with recent advances in economic evaluation (Lakdawalla and Phelps, 2021). In addition, we urge ICER to include the full impact of AD on patients and caregivers, including both healthcare and non-healthcare impacts. One recent study determined the cost-effectiveness of a hypothetical treatment for AD improved substantially from \$192,000 per QALY gained when considering only patient healthcare costs to \$107,000 per QALY gained when including healthcare costs and QALYs of patients and caregivers (Ito et al., 2021). When the same study analyzed both healthcare and non-healthcare factors, cost-effectiveness improved even more, from \$183,000 per QALY gained for patients alone to \$74,000 per QALY gained when considering both patients and caregivers (Ito et al., 2021). In its evaluation of donanemab, Lilly recommends that ICER apply a similar societal approach that includes the large caregiver burden unique to patients with AD. Also, because the patient and caregiver utilities used by ICER in its review of aducanumab (Neumann et al., 1999) lacked face validity, Lilly urges ICER to pursue alternative measures of quality of life for patients and caregivers, even relying on unpublished data or data from outside the U.S.

We believe incorporating these elements in ICER's review of donanemab will be in the best interest of both scientific rigor and patient care.

Sincerely,

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NATIONAL MINORITY QUALITY FORUM

January 19, 2022

ELECTRONIC SUBMISSION

Steven D. Pearson, MD, MSc, FRCP President, Institute for Clinical and Economic Review Two Liberty Square, Ninth Floor Boston, MA 02109

RE: NMQF Public Comment on ICER December 22, 2021 Draft Background and Scope of Work to Assess Beta-Amyloid Antibodies for the Treatment of Early Alzheimer's Disease

Dear Dr. Pearson:

The National Minority Quality Forum (NMQF) is submitting this comment to the Institute for Clinical and Economic Review (ICER) regarding the draft scoping document on assessing betaamyloid antibodies for early Alzheimer's disease (AD) that was released on December 22, 2021. NMQF is a 501(c)(3) not-for-profit research and advocacy organization based in Washington, DC. The mission of NMQF is to reduce patient risk by assuring optimal care for all. NMQF's vision is an American health services research, delivery and financing system whose operating principle is to reduce patient risk for amenable morbidity and mortality while improving quality of life.

Alzheimer's Disease (AD) is a fatal, degenerative brain disease that affects roughly 6.2 million individuals and is currently the 6th leading cause of death in the United States. Alzheimer's Disease is devasting to individuals diagnosed with the disease, as well as their families, caregivers and significant others. African Americans are two to three times more likely than non-Hispanic Whites to develop AD; and, Latinos are 1.5 times as likely. These disparities exist throughout all phases of AD. It is estimated that by 2030, nearly 40 percent of all Americans living with AD will be Black or Latinx.

In short, for communities of color in the United States – indeed worldwide – the stakes associated with ICER's assessment of current and potential treatments for Alzheimer's Disease cannot be higher.

NMQF has established the Institute for Equity in Health Policy and Practice to enable critical stakeholders to respond to these challenges in the context of centering structural and systemic health equity in every aspect of the American health services research, delivery and financing system. NMQF is committed to effective organization and management of system resources to improve the quality and safety of health care for the *entire* U.S. population, including – and not

ELECTRONIC SUBMISSION NATIONAL MINORITY QUALITY FORUM

Public Comment on ICER Draft Background and Scope of Work to Assess Beta-Amyloid Antibodies for the Treatment of Early Alzheimer's Disease January 19, 2022

excluding – racial and ethnic populations that are in the minority in the United States. Our engagements have always rested upon the foundation of health equity and health disparity elimination throughout the research, delivery and financing enterprise that is in service to families and communities in the United States.

As stated by President Joseph Biden in his Presidential *Executive Order On Advancing Racial Equity and Support for Underserved Communities Through the Federal Government*:

"Equal opportunity is the bedrock of American democracy, and our diversity is one of our country's greatest strengths. But for too many, the American Dream remains out of reach. Entrenched disparities in our laws and public policies, and in our public and private institutions, have often denied that equal opportunity to individuals and communities. Our country faces converging economic, health, and climate crises that have exposed and exacerbated inequities, while a historic movement for justice has highlighted the unbearable human costs of systemic racism. Our Nation deserves an ambitious whole-of-government equity agenda that matches the scale of the opportunities and challenges that we face.

It is therefore the policy of my Administration that the Federal Government should pursue a comprehensive approach to advancing equity for all, including people of color and others who have been historically underserved, marginalized, and adversely affected by persistent poverty and inequality. Affirmatively advancing equity, civil rights, racial justice, and equal opportunity is the responsibility of the whole of our Government. Because advancing equity requires a systematic approach to embedding fairness in decision-making processes, executive departments and agencies (agencies) must recognize and work to redress inequities in their policies and programs that serve as barriers to equal opportunity."

As stated in the general provisions of President Biden's Executive Order, "Independent agencies are strongly encouraged to comply with the provisions of this order." The National Minority Quality Forum believes that the organizations and individuals who constitute ICER's authorizing environment have an obligation to their stakeholders, members and beneficiaries to hold ICER's methods, values, policy statements and value assessments to a correspondingly high and responsive standard. Failure to do so can result in harms – whether intentional or unintentional – that cannot be reversed. That is a risk not worth taking.

We look forward to further discussions on these critical systemic issues.

Sincerely, Gretchen C. Wartman Vice President for Policy and Program Director, Institute for Equity in Health Policy and Practice Director, National Alliance for Brain Health and Awareness

Point32Health

January 19, 2022

Institute for Clinical and Economic Review 14 Beacon Street, Suite 800 Boston, MA 02108 Sent via email to: <u>publiccomments@icer-review.org</u>

Re: ICER Assessment of Beta-Amyloid Antibodies for Early Alzheimer's Disease

To Whom It May Concern:

On behalf of Point32Health, the combined organization of Harvard Pilgrim Health Care and Tufts Health Plan, we appreciate the Institute for Clinical and Economic Review (ICER) conducting an assessment of the comparative clinical effectiveness and value of the beta-amyloid antibodies donanemab (Eli Lilly & Co.) and lecanemab (Eisai Inc.) for the treatment of Alzheimer's disease, along with aducanumab (Aduhelm[™], Biogen) should new clinical evidence become available. We strongly support all efforts to ensure a thorough review of the safety and efficacy of new drug therapies and we thank ICER for the opportunity to provide feedback during the Open Input period.

Point32Health is a leading health and wellbeing organization. Building on the quality, nonprofit heritage of our founding organizations, Tufts Health Plan and Harvard Pilgrim Health Care, we leverage our experience and expertise to help people find their version of healthier living through a broad range of health plans and tools that make navigating health and wellbeing easier for our 2.2 million members across New England.

Alzheimer's disease is a progressive and debilitating condition that affects memory, thinking and behavior. Point32Health is committed to supporting our communities in their fight to end Alzheimer's. We invest in efforts that help expand awareness, that advance research on preventative care and treatment solutions, and that identify and implement systemic and innovative programs to improve the lives of those living with Alzheimer's and their caregivers. Our past and current leaders have served on the Alzheimer's Association Board of Directors, and we are consistently a top fundraiser for the Association, with many of our colleagues participating in their annual awareness walk. We also have Alzheimer's Association staff embedded into our organization to help families navigate their health care needs when a family member is impacted by this debilitating disease. While we are eager for a treatment that will slow or even reverse the impacts of this disease, as explained in the attached letter, aducanumab is neither safe nor effective.

A key issue with the approval of aducanumab, and with the upcoming requests for approval of donanemab and lecanemab, is the use of a surrogate marker rather than clinical improvement as an

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endpoint. These treatments reduce beta amyloid in the brain as shown by imaging studies or analysis of cerebrospinal fluid. However, there is no clear evidence that this reduction in amyloid produces cognitive improvements and the aducanumab studies failed to clearly demonstrate improved functional abilities. Surrogate markers as evidence of impact on disease must only be used when that biomarker has clearly and definitively been shown to be the cause of the disease or to be a clear marker of clinical improvement. Beta amyloid does not yet meet that criteria. Instead, these treatments have been associated with side effects that may further accelerate cognitive and/or functional decline.

Another flaw in the studies used to approve aducanumab was the paucity of enrollment of diverse populations. Alzheimer's disease impacts people of all racial and ethnic backgrounds and trials of treatments must include adequate representation of people of color. The current aducanumab studies provide no evidence relevant to the treatment of a Black or Brown patients and any studies presented to the FDA for approval for the newer agents need to include diverse representation. Alzheimer's is an unfortunately common disease, making recruitment across subsets of the population possible.

More longitudinal studies are also critical to evaluating the success of these treatments. Longer studies are designed to assess true clinical markers, such as memory, language, and functional abilities.

Attached please find a copy of the detailed comments Point32Health submitted to the Centers for Medicare and Medicaid Services (CMS) on August 11, 2021 in response to their initiation of a national coverage determination (NCD) analysis for Monoclonal Antibodies Directed Against Amyloid for the Treatment of Alzheimer's disease. The attached letter includes a cover letter from Point32Health's Chief Medical Officer for Commercial Products and Neurologist, Claire Levesque, MD, as well as the following sections:

- I. Point32Health and its Support of Alzheimer's Patients
- II. Safety Concerns with Aduhelm
- III. Lack of Efficacy in Aduhelm
- IV. Medicare's Prohibition from Covering Unsafe, Unproven Treatments

The health and well-being of our members is at the heart of every decision Point32Health makes and Alzheimer's disease is very personal to many of us at Point32Health. Our priority is to provide our members with coverage for effective and safe treatments that are based on scientific evidence. Accordingly, we take careful consideration of the risks associated with any drug before moving forward with a coverage decision. After thorough review of the available clinical data on the efficacy and safety of aducanumab, Point32Health concluded that it is experimental and investigational. We consulted with our internal resources, as well as our regional providers who offer extensive expertise in this area, in making this clinical determination. The external experts we consulted with were unanimous in their recommendation that helped inform our decision. Further, the low utilization of the treatment and the paucity of requests to our health plan for coverage to date confirms that the neurological community does not view this treatment as proven to be beneficial to their patients.

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While the need for an effective new treatment for Alzheimer's disease is indisputable, shortcuts to solutions are not a fair response to the patients and families impacted by this terrible condition. We appreciate your consideration of this feedback during ICER's Open Input Period.

Sincerely,

Kristi 1 Cenis

Kristin Lewis Chief Government and Community Affairs Officer Point32Health

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January 18, 2022

Institute for Clinical and Economic Review Two Liberty Square Ninth Floor Boston, MA 02109

To Whom it May Concern:

We write on behalf of Voices of Alzheimer's, a newly formed not-for-profit organization that aims to share the stories of people living with Alzheimer's and other dementias with the goal of inspiring and informing others on how to live well, tackle challenges and provide opportunities to advocate for change.

As the founders of Voices of Alzheimer's, we appreciate the opportunity to share our experiences with various medications and living with our Alzheimer's diagnosis as ICER prepares its review of donanemab, lecanemab and gantenerumab. Lilly specifically requested that we submit our responses to you for this process.

One of Voices of Alzheimer's primary goals is to encourage the development of effective therapies to cure, prevent, delay and better manage Alzheimer's and related dementias. Also we strongly encourage our peers to participate in clinical trials.

We have each been diagnosed with Alzheimer's. Our ages at diagnosis range from 42 to 69. Since learning of our diagnosis, we have each been prescribed multiple medications.

Two of our founding members have been long-term participants in the clinical trials for aducanumab (Aduhelm). Others have taken Namenda and Donepezil with a variety of success and side effects.

For each of us, the Alzheimer's diagnosis brought great personal change. One founder, Rebecca Chopp, stepped down as Chancellor of the University of Denver. Another, Jay Reinstein, left his position as Assistant City Manager for the City of Fayetteville. Anitra Mostacero, a senior master sergeant in the U.S. Air Force, was diagnosed at age 42.

We cannot overstate the importance of developing effective therapies to cure, prevent, delay and better manage Alzheimer's disease and related dementias. We strongly support and encourage early diagnosis.

Current research into vaccines and other preventive therapies is of the utmost importance to our entire community, as is an "AIDS-like" cocktail to attach amyloid, tau, and inflammation simultaneously.

The advent of medicinal advances significantly increases the importance of and need for an independent review of value and availability. We are happy to support this effort whenever possible.

We have individually responded to the four questions asked by ICER as part of its evaluation of these "mab" drugs. Our individual responses follow.

Once again, we very much appreciate the opportunity to share our experiences with ICER as it completes its review of donanemab, lecanemab and gantenerumab.

If it would be helpful, we would be delighted to meet with you to share our experiences with the disease and our hopes for therapeutic progress. Please feel free to contact us with any such opportunities.

Sincerely,

Founders, Voices of Alzheimer's

Rebecca Chopp, Phil Gutis, Anitra (Nia) Mostacero, Jay Reinstein, Geri and James Taylor