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May 10, 2021

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 reiterate and expand upon comments we made in our external review on ICER's Aducanumab for Alzheimer's Disease: Effectiveness and Value Draft Evidence Report.

We fundamentally disagree with the methodology and conclusions of ICER's report. Throughout the report, ICER's analysis fails to take into account the totality of scientific evidence and a number of factors that an approved therapy may have on an individual with the disease and their caregivers. The impact of these methodological decisions could have the effect of limiting an individual's access to aducanumab--a drug that could add weeks, months, or even years of active life for those affected every day by the crushing realities of Alzheimer's. Our deep concerns are outlined below.

### **Inaccurate Characterization of Scientific Evidence**

*ENGAGE and EMERGE.* In its effort to evaluate the cost effectiveness of aducanumab, ICER assumed blended efficacy of the ENGAGE and EMERGE trials. We dispute and question ICER's approach. EMERGE met its prespecified primary outcome and found in the high dose aducanumab group a 22% reduction in decline on the CDR-SB--an outcome that was evident even under the situation of early trial cessation.

The argument made by ICER that "the primary outcome of CDR-SB, while a validated scale, is not used frequently in clinical practice and thus the minimal clinically important difference has not been established" is misconstrued. The 2013 version of the draft FDA guidance for "Alzheimer's Disease: Developing Drugs for the Treatment of Early Stage Disease" recommended the CDR-SB as one potential approach to evaluate cognitive and functional change in individuals with MCI. The outcome in CDR-SB was significant, and the test is an accepted measurement of both cognition and function as a primary outcome. While the scale of this test maintains a restricted range, small changes can reflect a clinically meaningful alteration for people living with MCI. In addition, EMERGE showed statistically significant differences between drug and placebo on all secondary outcome measures, including a 40% slowing of functional decline in the ADCS-ADL (a test that quantifies activities of daily living). The Neuropsychiatric Inventory (NPI), which was an exploratory outcome measure, assesses behavioral changes common in Alzheimer's. The NPI showed an 87% reduction from baseline, with a

corresponding 84% reduction of caregiver burden. All of this evidence should be the key to ICER's primary analysis. Further, the ICER analysis fails to consider the data in the context of the trial circumstances, instead only evaluating the pooled analysis. For instance, pooled analysis of the CDR-SB assessment across both studies has a treatment effect of 62%; however, when you include the key secondary outcomes in the analysis, this treatment effect is 99%, which better reflects the totality of evidence for high-dose aducanumab. When looking at the data from ENGAGE, similar benefits were observed in the ENGAGE participants who were treated with the high dose for longer periods of time. Lastly, when combined with PRIME data, the positive ENGAGE trial, supportive EMERGE and PRIME data, and additional data from other trials point to an efficacy signal. Per FDA guidance, approval of a drug can be based on a single positive study and supportive evidence.

Taken together, these results provide insight into not only the effects on cognition but also function and behavior that would be impactful for individuals living with Alzheimer's and their caregivers. They underscore our reasons to believe that aducanumab meets the standard of evidence for efficacy and should be what ICER uses for its cost-effectiveness analysis.

*ARIA and Potential Harm.* ICER has mis-characterized the ARIA-E and ARIA-H data and mis-interpreted the weight given to it compared with the potential benefits of the therapy. ICER notes that 41.3% of participants experienced ARIA-E and ARIA-H compared with 10.3% in the placebo arm; that 74.0% of ARIA-E cases in the high-dose aducanumab arm and 89.7% of cases in the placebo arm were asymptomatic; and that most ARIA-E symptoms and MRI findings were mild or moderate in severity and transient (98% resolved) in the high-dose aducanumab arm. These data simply do not support ICER's conclusion that taking aducanumab has a "high certainty of harm."

ARIA is a manageable side effect of treatment and is far less threatening than complications of many routinely used therapies for other conditions, including cancer. The FDA's rigorous review of any potential treatment significantly weights the safety but does so in the context of the full data package and in the context of expert guidance. This guidance, and the routine management of ARIA, has been adopted by multiple beta amyloid trials. The Alzheimer's Association Research Roundtable Workgroup developed recommendations<sup>1</sup> on detecting and monitoring amyloid-related imaging abnormalities in amyloid-modifying therapeutic trials to protect participants, guide clinicians, and ensure that this research can continue. The FDA--whose mission is to protect public health--has adopted guidance, built upon these recommendations, for reasonable management of ARIA.

Furthermore, on behalf of the individuals living with and caring for those living with Alzheimer's, we take exception to the view that implementing ARIA monitoring and treatment is "challenging" as a sufficient reason to question approval or coverage of a therapy. Living with Alzheimer's without any disease-modifying therapy is far more challenging, and it is fatal.

### **Failure to Account for True Value**

The misunderstanding and misrepresentation of the scientific evidence surrounding aducanumab has a dramatic effect on ICER's assumption of the value attributed to the drug, as measured by the assumed QALY gain. For example, using only the evidence from EMERGE rather than the blended data from

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<sup>1</sup> Sperling RA, Jack CR, Black SE, Frosch MP, Greenberg SM, et al. Amyloid-related imaging abnormalities in amyloid-modifying therapeutic trials: Recommendations from the Alzheimer's Association Research Roundtable Workgroup. *Alzheimers Dement* 2011;7(4):367-385.

both ENGAGE and EMERGE would result in a significantly higher assessed gain in QALY from aducanumab, resulting in a cost-effectiveness price about three times higher. Using the data for participants who received the highest dose of aducanumab in EMERGE, the QALY gain would likely be even greater. Such a dramatic difference underscores our concern about using blended data for this analysis, especially since it could have a profound effect on whether patients will have access to the drug.

It should be noted that this significant QALY difference is only over the interpretation of the scientific data. ICER's threshold analysis still relies on a rigid, inflexible, narrow--and in our view, outdated--formula that looks solely at direct patient costs instead of a valuation more appropriately suited to therapies for Alzheimer's disease and the long-term value of such a therapy. Alzheimer's disease presents unique issues and challenges to traditional cost-effectiveness analyses. While ICER acknowledges some of these challenges--and does attempt to include a broader "modified societal perspective" in the report--we are troubled that a more serious effort was not made to account for the full range of value that an Alzheimer's therapy would bring or the effect this failure might have on patient access to the drug.

What follows are several aspects of value that we believe should be taken into account in a cost-effectiveness analysis of Alzheimer's drugs. We strongly urge ICER to revise its analysis prior to the July 15 public meeting to incorporate this broader and more appropriate assessment of value. And we strongly recommend the appraisal committee vote to give these aspects a very high priority in judging the long-term value of an Alzheimer's treatment.

*What Patients and Caregivers Value:* ICER's formulation fails to take into account the value of what is truly important to those living with the disease and their caregivers. A systematic review of studies<sup>2</sup> found that patients and caregivers value outcomes such as maintaining an individual's independence and identity--that is, observable effects on their daily life. While ICER incorporates cognitive test scores from the clinical trials on aducanumab in determining cost-effective pricing, these scores can only be faint proxies for what individuals and caregivers truly value: the impact on how they are able to live on a day-to-day basis. ICER does not incorporate these values into the assessment.

*Caregiver Burden.* Alzheimer's places a huge burden on caregivers. If ever there was a disease or condition for which the value of a drug to caregivers must be taken into account, Alzheimer's disease is it. The care required of family and friends of those living with the disease is more intense and broader in scope than for caregivers of those with other conditions. Compared with other caregivers, dementia caregivers have twice as many substantial emotional, financial, and physical difficulties. Depression is significantly higher. They are twice as likely to say their health has worsened as a result of caregiving. And, those who contribute to the care of someone with dementia are 28% more likely than other adults to eat less or go hungry because they cannot afford food.

A drug therapy that slows the progression of Alzheimer's disease--extending the period of time when individuals with the disease remain in a stage where they have some level of independence and an ability to significantly contribute to their own care--provides an enormous value to caregivers, which

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<sup>2</sup> Tochel C, Smith M, Baldwin H, Gustavsson A, Ly A, et al. What outcomes are important to patients with mild cognitive impairment or Alzheimer's disease, their caregivers, and health-care professionals? A systematic review. *Alzheimers Dement (Amst)* 2019;11:231-247.

must be taken into account in cost-effectiveness analyses. ICER's modified societal perspective includes medical and productivity costs of the primary caregiver--but does not fully account for what caregivers value and the value a drug would bring to caregivers, such as a reduction in distress and burden. In fact, the additional QALY gain under the modified societal perspective appears to be only about 0.005. Other analyses have found the QALY gain attributable to caregiver value significantly higher, indicating that ICER is not taking into account the full and true value to caregivers.

*Unmet Need.* The unmet need for those living with Alzheimer's and those who will develop Alzheimer's is critical. No disease modifying treatments exist, and for more than a decade there have been a series of initially promising but ultimately ineffective potential disease modifying therapies. Aducaumab represents a real advance for those affected by this devastating disease. It is not a cure, nor even the most successful possible therapy. But it would provide as many as several years of positive benefits for a devastating disease that places an enormous burden on caregivers--and for which there is no alternative. In other words, addressing an unmet need has value in and of itself and should be accounted for.

*Innovation.* The first-ever disease modifying therapy has value in another way: Innovation. Rarely is a first-of-its-kind treatment--for any condition--a panacea or cure-all. But it often does spur the research into and development of additional and better therapies. For example, approval and coverage of the first reductase inhibitor for lowering LDL cholesterol--and thus delaying the onset of heart disease, the leading cause of death in the United States--spurred the development of at least six additional therapies. There were questions surrounding the effectiveness of the first treatment for HIV, but AZT's approval and coverage stimulated the scientific community to develop additional treatments and combination therapies that have now resulted in a nearly two-thirds decline in the number of HIV deaths since 2000. Even with Alzheimer's disease, approval of the first symptomatic treatment (tacrine) led to the development and approval of better and safer symptomatic drugs.

This innovation value is crucial for people living with Alzheimer's and future generations of individuals who will develop Alzheimer's. Without the first, there cannot be the second or third or fourth, each improving on the earlier treatments. We recognize this value cannot be measured in terms of short-term patient costs, but we oppose the systematic exclusion of innovation from determinations of value.

*Earlier Diagnosis:* Even without a disease-modifying therapy, the benefits of an early diagnosis of Alzheimer's are well-known. Early diagnosis allows individuals with the disease and their caregivers to better manage medications, build a care team, manage comorbidities, receive counseling and other support services, create advance directives, and address driving and safety concerns. Studies have also shown that health and long-term care costs are lower among people diagnosed earlier.<sup>3</sup> Unfortunately, too many individuals with Alzheimer's are diagnosed too late--if they are diagnosed at all. Many primary care physicians say they doubt the value of diagnosing a condition for which there are no treatments, and nearly half of primary care physicians in one survey<sup>4</sup> say they sometimes choose not to even assess an individual's cognition because, if the individual is eventually diagnosed, treatment

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<sup>3</sup> See, for example: Lin PJ, Zhon Y, Fillit HM, Chen E, Neumann PJ. Medicare expenditures of individuals with Alzheimer's disease and related dementias or mild cognitive impairment before and after diagnosis. *J Am Geriatr Soc* 2016;64(8):1549-1557; and Alzheimer's Association. 2018 Alzheimer's Disease Facts and Figures. *Alzheimers Dement* 2018;14(3):367-429.

<sup>4</sup> Alzheimer's Association. 2019 Alzheimer's Disease Facts and Figures. *Alzheimers Dement* 2019;15(3): 321-387.

options are limited. The approval and coverage of a disease-modifying therapy for Alzheimer's would drive earlier diagnosis and thus accrue benefits, even if the direct effect of the drug were limited.

This is of particular importance among diverse populations. Evidence suggests Blacks and Hispanics on average are diagnosed at a much later stage than Whites. This raises profound health equity concerns around access to care, quality of care, and financial burden. As the first-of-its-kind treatment, aducanumab's value in driving earlier diagnosis should not be ignored, and this value should be taken into account.

*Equity Impact:* In addition to the potentially greater value of an earlier diagnosis that the approval and coverage of aducanumab may have on traditionally underserved populations, the treatment itself could have tremendous value in addressing the disproportionate impact of Alzheimer's. Blacks are about twice as likely and Hispanics are about one and a half times as likely as Whites to develop Alzheimer's. In other words, relatively, this drug could have a greater value on the Black and Hispanic communities than the White population. ICER's formula does not take into account the value of reducing health disparities between those who are at higher risk of developing Alzheimer's and those who are not.

### **Conclusion**

As indicated by our comments in the external review and this letter, the Alzheimer's Association believes ICER's analysis has deep flaws with respect to both the scientific evidence and the assessment of value. It dismisses or ignores the far-reaching effects of the disease and the wide-spread benefit aducanumab would have for millions of individuals and families. The consequences could be dire: it could serve to deny millions access to a necessary treatment and to a real advancement in the treatment of Alzheimer's. We strongly urge ICER to carefully consider the input contained in these comments and amend its analysis accordingly.

Thank you for the opportunity to comment. Please do not hesitate to contact Matthew Baumgart, Vice President of Health Policy, at [mbaumgart@alz.org](mailto:mbaumgart@alz.org) or 646.849.9978 if we can be of additional assistance.

Sincerely,



Joanne Pike, DrPH  
Chief Strategy Officer

*The Alzheimer's Association received 0.89% of its total 2020 contributed revenue from the biotechnology, pharmaceutical, diagnostics, and clinical research industry, including 0.15% from Biogen and Eisai. For more information, see [alz.org/transparency](http://alz.org/transparency).*