abbvie

Nov 10, 2020

ICER Aducanumab for Alzheimer's Disease Draft Scoping Document – Response to Request for Public Comments

AbbVie supports an evidence-based value assessment paradigm that reflects the unique and diverse criteria of stakeholders impacted by the assessment and those making healthcare decisions, and that preserves shared decision-making between patients and their healthcare providers. We are committed to preserving the personhood of those living with Alzheimer's Disease (AD). We fight side-by-side with patients, care partners and clinicians against the often-unrelenting burden of AD. We believe effective treatments, including disease modification therapies, can be attained – and even with the inevitable setbacks – delivering science that takes us one step closer to meaningful change. As such, AbbVie appreciates the opportunity to provide comments on the ICER Draft Scoping Document for the Assessment of Aducanumab for Alzheimer's Disease. Please see below AbbVie's brief comments for your consideration and clarification.

Scope of Clinical Evidence Review

Population: In the scoping document, ICER indicates that the population under evaluation is adults with early AD, including MCI due to AD and mild AD dementia. In 2018, FDA issued an industry guidance for developing drugs for early Alzheimer's Disease in which it classified early AD into four different stages, including Stage 1 where patients only have pathological changes with no clinical impact.[1] The definition of early AD in this scope appears to be relatively narrower than the FDA classification. Please clarify how early AD defined in this project maps against the FDA classification.

Outcomes: The list of the outcomes of interest is extensive. ICER lays out how it intends to evaluate cognition and activities of daily living (ADL) in the scoping document. For ADL, the suggested scale AD Cooperative Study – Activities of Daily Living (ADCS-ADL) may be less sensitive to the early AD population and therefore we recommend that ICER uses the MCI version (ADCS-ADL-MCI) for assessment. Also, it remains unclear how ICER plans to assess other listed outcomes, e.g., "ability to maintain independence and autonomy", "emotional wellbeing", "symptom progression", and "maintenance of identity and personality". More details on these outcomes, e.g. information on scales used for assessments, would be helpful. In addition, one domain that is important to AD and seems to be missing from the list is behavioral change among these patients. We strongly recommend that ICER assesses behavioral change as one of the meaningful outcomes.

Scope of Comparative Value Analyses

In general, AbbVie agrees with ICER's approach as described in the *scope of comparative value analyses* section to use a cohort model to track disease severity (MCI due to AD, Mild AD, Moderate AD and Severe AD), need for full-time care and survival. We would like to understand what measure(s) would be used to define health states in the model to track AD progression. Would such measure(s) include cognition, function and/or other domains? While AbbVie recognizes that details pertaining to modeling are limited given the brevity of the scoping document, we strongly recommend that ICER adopts a comprehensive framework to capture the potential benefit of the assessed treatment. For example, such a model may also need to incorporate behavioral change in its track of disease progression if evidence exists.[2]

ICER states that the base case model would only include direct medical cost. Indirect cost such as productivity impacts, caregiver impacts will only occur, if "data permitting", in a separate modified societal perspective scenario analysis. AbbVie understands that ICER is still in its initial stage of data gathering. However, we urge ICER to consider incorporating caregiver impacts into the primary base case model for the cost-effectiveness analysis. As outlined in the scoping document, the impact of AD on caregivers is substantial. It is estimated that in 2019, caregivers in the US provided $244 billion of unpaid care to AD patients as compared to $305 billion of direct medical cost.[3] In addition, caregivers of AD patients report significant worse quality of life.[4] Since AD is associated with significant economic and humanistic burden for caregivers, it is important to consider caregiver impacts for a comprehensive assessment of the value associated with the treatment.

We believe that the incorporation of these recommendations will allow for a more comprehensive and robust assessment of the value for treating AD.

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November 10, 2020

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

RE: Public Comment - Draft Scoping Document outlining for review of the comparative clinical effectiveness and value of aducanumab (Biogen) for Alzheimer's disease

Dear Dr. Pearson,

Drs. Bhattacharjee and Doub appreciate the opportunity to provide comments in response to the Institute for Clinical and Economic Review (ICER) Draft Scoping Document on the assessment of clinical effectiveness and value for aducanumab (Biogen) for adults with early Alzheimer's Disease (AD), including MCI due to AD and mild AD dementia.

Timing of Assessment

As there is no disease modifying therapy approved yet by the FDA and we are still waiting for the pending priority review of the Biologics License Application concerning aducanumab (Biogen, Inc.) we believe this review is premature. We share the same opinions presented by Knopman et al. (2020) regarding the inconclusively of aducanumab given the positive results of EMERGE and the overall failure of ENGAGE trial.(1) Although post-hoc analysis of ENGAGE trial demonstrated a positive effect in a specific sub-population that received all high dose aducanumab treatments, post-hoc analyses cannot serve as a reliable evidence as they are not comparable to the predictive power of the *a-priori* primary trial analysis.(2) In addition, there are other differences in EMERGE and ENGAGE trials that must be addressed including differences in placebo group performance [e.g. Clinical Dementia Rating Scale Sum of Boxes (CDR-SB)].(2) The assessment should be postponed until more conclusive information regarding aducanumab is made available through completion of the phase 3b study (NCT04241068).(3)

Underserved Population

It is estimated that amongst adults 65-years of age and older with AD, approximately 14% are African American and 12% are Hispanics.(4) Specifically, ICER should consider racial disparities present in two key trials used to evaluate efficacy of aducanumab (Biogen, Inc.) among AD patients in the United States. In both EMERGE and ENGAGE trials, baseline demographics of placebo, low-dose, and high-dose groups are heavily weighted in individuals of white race followed by Asians.(2) Therefore, efficacy, safety, and accessibility amongst underrepresented race/ethnic groups must be evaluated.

Comparators

ICER proposes to develop an economic model to assess the lifetime cost effectiveness of aducanumab compared to best supportive care (BSC). Comparing aducanumab to BSC might not be the appropriate comparator for this analysis. Approved pharmacological treatment options for AD (such as donepezil, rivastigmine, galantamine and memantine) should be considered as comparators as it will reflect the real-world treatment utilization, initiation and safety. For example, in one of our recently published studies (5), the final study cohort consisted of 21,558

Medicare beneficiaries with AD (13,837 were donepezil initiators, followed by 4,884 memantine, 2,235 transdermal rivastigmine, 355 galantamine, and 247 oral rivastigmine initiators). This study demonstrated that donepezil was associated with a lower risk of all-cause mortality compared to memantine, oral rivastigmine and transdermal rivastigmine.(5) Additionally, we observed that the overall all-cause hospitalization risk for the different anti-AD medication initiation was significantly different for the intention-to-treat analysis, but did not differ for the as-treated-analysis.(5) Thus, based on this real-world evidence, treatment utilization/initiation as well as comparative safety differed among the different anti-AD medications.

Perspective of the analysis

While it is understandable that ICER proposes to conduct the base-case analysis from a health care system perspective, it is perhaps better to use societal perspective that considers the productivity impacts, caregiver impacts, and other indirect costs as the base-case analysis. According the 2020 Alzheimer's Association report, "family members and friends provided nearly $244 billion in unpaid care to people with Alzheimer's and other dementias in 2019". (6) This high caregiver burden, along with other important aspects of AD (such as activities of daily living, instrumental activities of daily living) must be considered for the comparative value analyses.

Another important clarification warranted for the proposed analysis is which particular health care perspective will be considered to develop the base-case analysis. The US health care system is complex and it is estimated that approximately 67% ($206 billion) of the current expenditures of dementia are covered by Medicare, placing a substantial burden on the near-universal payer for older US adults.(6) However, other payers (e.g.- private insurance) also experience high burden of AD care.

We thank ICER again for the opportunity to engage in this review process and allowing us to provide commentary.

Sincerely,

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November 10, 2020

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 aducanumab.

Background

The Alzheimer's Association appreciates ICER's acknowledgment of the role of caregivers in Alzheimer's disease as well as the impact of the disease on them. Caregivers play a pivotal role as they attend to the daily health and functioning of a person with Alzheimer's. In fact, many providers have noted that caregiver involvement is a determinative factor in the success of the management of the care of a patient living with dementia. We believe that since caregivers are integral to the success of best supportive care, ICER must consider the impact a treatment may have on a caregiver's health and quality of life.

We would also like to take this opportunity to clarify some scientific matters mentioned in the document.

- ICER states that the "**clinical diagnosis** of AD is divided into three periods: preclinical disease, mild cognitive impairment (MCI), and Alzheimer's dementia" [emphasis added], citing the Alzheimer's Association's *2020 Alzheimer's Disease Facts and Figures*. In fact, the three-phase continuum refers to the 2011 NIA-AA Research Framework and the preclinical phase is intended for use in an Alzheimer's research context, and not yet for clinical diagnostic purposes.
- ICER refers to "genetic defects" in some individuals, such as a "carrier of the apolipoprotein E [ApoE] e4 allele." Everyone inherits one of three forms (alleles) of the APOE gene — e2, e3, or e4. While having the e4 form of APOE increases one's risk of developing Alzheimer's in certain populations, it is not a genetic defect; it is simply a variant.
- The document states, "Over time, subtle cognitive changes begin to occur and certain biomarkers in the cerebrospinal fluid (CSF) such as increased CSF tau protein levels become apparent and imaging biomarkers such as the presence of amyloid on positron emission tomography (PET) scans may also be detected; such CSF and imaging biomarkers can be used to differentiate AD from other dementias." This phrasing suggests that the presence of biomarkers follows the preclinical stage, when in fact biomarkers of the disease are present (and apparent through CSF and PET imaging) in the preclinical stage.
- ICER states that "Treatment of AD remains largely supportive, including creation and implementation of individualized dementia care plans…caregiver education and support, and referral to community-based organizations for services (e.g., adult day care, caregiver training, etc.)." We recommend that ICER add care navigation and care coordination to the supportive services it considers.
- In its discussion of available therapies, we note that in addition to those listed, a fifth medication, which is a combination of the cholinesterase inhibitor donepezil with memantine, is also available and was approved in 2014.

Scope of Clinical Evidence Review

While we support ICER's review of randomized controlled trials (RCTs), we also appreciate its intent to consider high-quality systematic reviews, high-quality comparative cohort studies, input from patients and patient advocacy organizations, data from regulatory documents, information submitted by manufacturers, and other grey literature. Randomized controlled trials are simply not long enough in duration to measure much of what is most important to persons living with Alzheimer's and caregivers. The Alzheimer's Association regularly hears from constituents that independence and quality of life--often not measured in RCTs--are far higher priorities than amyloid loads or scores on cognitive assessment tools.

Populations

The scoping document states that the population of interest for this review is adults with early AD, "including MCI due to AD and mild AD dementia." The word “including” could be interpreted as "some but not necessarily all," where the Alzheimer's Association believes that MCI due to AD and mild AD dementia should be the entire scope of ICER's analysis, given the populations tested in the clinical trials. We respectfully request that ICER clarify the meaning of this sentence and the population of interest and consider where this phrasing appears elsewhere in the document.

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 encourage ICER to consider that several of these outcomes are interconnected and related. For instance, maintaining independence influences one's quality of life. We also encourage the addition of “ability to communicate” to the list of “Patient-important outcomes.”

Under "Other Outcomes," we strongly encourage ICER to add non-cognitive or behavioral symptoms, such as managed or reduced depression, aggression, apathy, and sleep disturbances. Caregivers consistently cite the successful management of these symptoms as very important to their quality of life.

Scope of Comparative Value Analyses

ICER indicates its intent to approach its base-case analysis with a health care system approach and only consider direct medical care costs. We respectfully request that ICER clarify whether that perspective includes long-term care costs. Given the significant use of long-term care services by persons with dementia -- and the potential for a therapy to delay placement in a nursing home -- we encourage ICER to consider these costs as “medical care costs.” Further, most literature referring to "direct" medical costs includes all medical costs incurred by individuals. We want to ensure that is the case here. That is, it would be a mistake to define “direct” medical costs as only those costs related to cognitive issues. Persons with dementia have a high prevalence of other chronic conditions. The costs associated with these chronic conditions are exacerbated by the presence of a cognitive impairment and could be significantly mitigated with a treatment. Therefore, they should be included when evaluating the impact on “direct” medical costs.

With regard to "best supportive care," we encourage ICER to consider a definition beyond what may be the status quo in the absence of an equivalent treatment on the market and instead consider the evidence-based best practice care. There are many interventions that positively affect quality of life even if their adoption is not yet widespread. As an example, we refer ICER to the 2018 Dementia Care Practice Recommendations, which are

evidence-based recommendations on the best care delivery in facilities and the community. We also refer ICER to dementia care management programs such as UCLA's Alzheimer's and Dementia Care (ADC) Program.

ICER intends to explore the potential health care system budgetary impact of treatment in a separate analysis. Similar to our above comment, the Alzheimer's Association wants to ensure that evaluation of the impact on the "health care" system includes the impact on Medicaid and the long-term care system, as well as the impact on family budgets. Given the significant long-term care costs incurred by individuals with dementia and the high level of out-of-pocket spending by families over the course of the disease, we believe it is important these costs are included. Most individuals in the target population for this drug are not currently users of long-term care services, and an improvement in the MCI and early dementia stage could elongate the stages of the disease in which nursing home care is not needed and reduce the length of stages of the disease in which it is needed.

Identification of Low-Value Services

We respectfully request that ICER provide examples of "services used in the current management of early AD beyond the potential offsets that arise from a new intervention." With that clarification, we would be happy to provide information on services that could be reduced, eliminated, or made more efficient.

Additional Remarks

We also note that the availability of a therapy is very likely to drive rates of diagnosis, regardless of the population for whom aducanumab is indicated. Currently, Alzheimer's is grossly underdiagnosed -- some estimates indicate it could be as high as half of all cases remain undiagnosed -- and without a diagnosis, individuals cannot plan and make choices about care or participate in clinical trials -- benefits beyond the possibility of immediately receiving a therapeutic agent. If aducanumab is approved, many individuals for whom the drug is not indicated will nonetheless benefit because they will receive a diagnosis. Most notably, this will allow for better management of co-occurring chronic conditions, which would reduce costs to the system even if they do not receive the drug.

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

Sincerely,

Joanne Pike, DrPH
Chief Strategy Officer

Biogen welcomes the opportunity to comment on ICER's *Aducanumab for Alzheimer's Disease Draft Background and Scope*. Alzheimer's Disease (AD) is the 6th leading cause of death in the U.S. and continues to be the number one fear for Americans over the age of 60.[1,2] As a pioneer in neuroscience, Biogen is committed to the development of treatments that may change the course of AD and help AD patients and their caregivers live longer and healthier lives. Given the burden of AD, its broad impact and evolving treatment landscape, value assessment needs to evolve to capture this. We appreciate ICER's continued efforts to incorporate elements important to both patients and caregivers and would like to highlight a few important considerations:

1. **In Alzheimer's disease, the societal perspective should be the base case, prioritizing and capturing caregiver's quality of life and costs.**
2. **We agree with ICER that the population should be MCI due to AD and mild AD dementia.**
3. **Focus this clinical and economic assessment on the finding that sufficient exposure to high dose aducanumab reduced clinical decline across multiple clinical endpoints.**
4. **We agree with ICER that the comparison should be aducanumab in addition to best supportive care vs. best supportive care.**
5. **Potential health system budget impact analysis should use population estimates based on intended use and realistic utilization uptake.**

Below, we expand on our points on the clinical impact of aducanumab on patients and the costs of AD, with the inclusion of Tables and Figures in the Appendix.

Introduction

Alzheimer's disease places an enormous burden on patients and their caregivers and the impact on society is significant. Ultimately fatal, AD is an insidious disease in which pathology begins to accumulate in the brain years before the onset of symptoms. AD continues to increase and by 2050, there will be an estimated 13.8 million people age 65 and older with Alzheimer's dementia.[3] This presents a catastrophic public health crisis as patients spend much of the time with this disease in disability, dependent on caregivers. AD contributes to a massive reduction in both caregiver and patient quality of life that stems not only from substantial physical infirmity but severe psychological deterioration of well-being.[4,5] In addition, while 16% of AD costs are incurred by the healthcare system, the majority of this nearly $550 billion per year is borne by patients and their families.[6,7,8] Social equity issues also present a key challenge for AD patients. AD prevalence is higher in Hispanic and African American populations. Women are disproportionately affected by AD, making up nearly two thirds of those with AD in the U.S. and approximately 75% of all caregivers.[9]

As potentially the first treatment indicated to delay clinical decline in AD, aducanumab represents a major step forward: if approved, aducanumab could substantially alleviate disease burden on patients and their caregivers as well as society. The failure rate in AD drug development is 99%, and the failure rate of drugs aimed at modifying the course of AD is 100% to date.[10] As a result, there are currently no available therapies that slow or delay clinical decline in AD, including mild cognitive impairment (MCI) due to AD.[11,12] Aggregation of the amyloid beta (Aβ) peptide in the brain is a pathological hallmark of AD, and is widely hypothesized to initiate a pathological cascade of events that ultimately manifest as clinical AD. Aducanumab selectively targets aggregated forms of Aβ. If approved, aducanumab will transform the current AD treatment landscape and may catalyze the development of novel diagnostics and therapeutics.

Biogen

Recommendations

1. In Alzheimer's disease, the societal perspective should be the base case, prioritizing and capturing caregiver's quality of life and costs.

ICER should capture the impact of AD on caregivers and reinforce caregiver impact on AD outcomes. If there is any assessment where ICER should directly consider benefits outside of the healthcare system, it is AD. ICER states in the 2020 Value Assessment Framework that they will consider costs outside of the healthcare system if the incremental cost-effectiveness ratio changes by > 20%.[13] Eighty-four percent of AD costs and the majority of disease burden lie outside of the healthcare system (see Figure 6), including 42.3% in direct non-medical costs representing out-of-pocket costs and 41.7% from lost wages.[14,15] In 2019, 16.3 million informal caregivers provided 18.6 billion hours of unpaid care equivalent to $244 billion.[16] These spillover consequences are significant: in 85% of the analyses to date, adding AD spillover cost or health effects improved cost-effectiveness or made an intervention cost saving.[17] In addition, the value of greater independence for an AD patient is of such consequence to society, that this should inform higher willingness to pay thresholds for AD.[18,19]

While ICER has not historically made provisions for including caregiver QALYs, it is important this is included in the base case of this AD assessment. ICER highlighted caregiver impact as an outcome of interest in the PICOTS framework of the *AD Draft Scoping Document*, necessitating a direct account for the significant non-medical costs and decreased QALYs of caregivers. Approximately three-quarters of AD patients live at home and receive care informally, and half of these patients have more than one caregiver.[20] Time spent on patient care significantly affects caregivers' quality of life with 30% of caregivers diagnosed with depression, compounded by anxiety and burden, which increase over time.[21] Moreover, the stress of caregiving has been linked to various health conditions including hypertension, impaired immune function and coronary heart disease (see Figure 7). This increases the risk of hospitalization in caregivers: owing to this, family members caring for AD patients have higher annual healthcare costs when compared to the general population ($7,168 vs $6,301).[22,23,24]

Lastly for outcomes, ICER should look at other endpoints, recognizing that the EQ-5D does not reflect the core outcomes set for AD. The EQ-5D can be insensitive to disease changes, and it does not capture patient-important outcomes such as dignity, autonomy and control, satisfaction with relationships, and having meaningful activities; there is also poor correlation between caregiver proxy ratings and patient self-reported QoL.[25,26,27,28]

2. We agree with ICER that the population should be MCI due to AD and mild AD dementia.

In the EMERGE and ENGAGE studies, aducanumab was evaluated in patients diagnosed with early-stage AD, defined as MCI due to AD or mild AD dementia, in whom amyloid pathology was confirmed. Hence, the target population for aducanumab is limited to patients with MCI due to AD or mild AD dementia with confirmed amyloid pathology (shown in Table 3). Those with MCI or dementia due to other causes are *not* part of the group for whom aducanumab would be appropriate. Additionally, any modeling of the natural history of AD needs to be in a population with confirmed Aβ pathology.

3. Focus this clinical and economic assessment on the finding that sufficient exposure to high-dose aducanumab reduced clinical decline across multiple clinical endpoints.

Aducanumab reduced clinical decline in patients with early-stage Alzheimer's disease, a first in the history of AD drug development. One fundamental learning in the clinical experience of aducanumab is that increased

exposure to high-dose aducanumab is associated with greater removal of Aβ pathology from the brain and improved clinical outcomes:

- **PRIME:** The Phase 1b study of aducanumab (PRIME) used fixed doses ranging from 1 mg/kg to 10 mg/kg and showed a dose-dependent reduction in Aβ plaque deposition as assessed by amyloid PET imaging as well as a dose-dependent slowing of clinical decline over the 54-week placebo-controlled period. Among those dosed with aducanumab during the placebo-controlled period of PRIME, Aβ plaque levels continued to decline in a time- and dose-dependent manner in the long-term extension period. Between weeks 110 and 222, Aβ plaque levels generally continued to decline in a dose-dependent manner, and mean Aβ plaque levels in the 10 mg/kg fixed dose group reached and remained at a level below the quantitative cut-point that distinguishes between a positive and negative amyloid PET scan. These Phase 1b results led to the selection of two dose regimens (low and high) in the Phase 3 EMERGE and ENGAGE studies.
- **EMERGE:** The high-dose regimen of aducanumab in the EMERGE study was associated with a robust removal of Aβ pathology from the brain and met both the pre-specified primary endpoint (CDR-SB) and all three secondary endpoints (MMSE, ADAS-Cog 13, ADCS-ADL-MCI) .[29] This is the first pivotal study in the history of AD drug development to demonstrate a statistically significant slowing of clinical decline.
- **ENGAGE:** In contrast to the EMERGE study, the ENGAGE study did not meet the primary or secondary endpoints. We believe that the differences between EMERGE and ENGAGE can mostly be accounted for by a greater level of exposure to high-dose aducanumab in EMERGE. Specifically, compared to the EMERGE study, fewer individuals in the ENGAGE study received the intended dosing regimen of high-dose aducanumab. Accordingly, the magnitude of amyloid removal from the brain in ENGAGE was less than that observed in EMERGE. In a post-hoc analysis, we found that patients in ENGAGE who had the opportunity to receive the intended dosing regimen of high-dose aducanumab (10 mg/kg) experienced a slowing of clinical decline similar to the comparable population in EMERGE in both the primary and secondary endpoints.

Therefore, it is important that ICER reflect the efficacy observed in EMERGE in both the evaluation of the clinical evidence as well as the comparative value analysis modeling. See trial endpoints in Table 1 and Figures 1-4.

4. The comparison should be aducanumab in addition to best supportive care vs. best supportive care.

Aducanumab will be used in addition to best supportive care and therefore, the most appropriate comparison is aducanumab plus best supportive care vs. best supportive care, as reflective of the trial population.

5. Potential health system budget impact analysis should use population estimates based on intended use and realistic utilization uptake.

The U.S. population of patients with early-stage AD that may benefit from aducanumab is estimated to be 1.4M, shown in Figure 5.

In summary, this could be one of the most important assessments ICER undertakes, with implications to patients and caregivers that go far beyond the healthcare system. It will be important for ICER to ensure that value assessment methods adequately reflect the devastating effects AD has on patients, their caregivers and society. This is a disease with an impact that transcends the narrow health sector. The methods and perspectives utilized for this assessment need to recognize this reality.

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Appendix

Table 1: EMERGE: Primary and secondary endpoints from final data set at week 78

	Placebo decline (n=548)	Difference vs. placebo (%)[a] p-value	
		Low dose (n=543)	High dose (n=547)
CDR-SB	1.74	**-0.26** (-15%) 0.0901	**-0.39** (-22%) 0.0120
MMSE	-3.3	**-0.1** (3%) 0.7578	**0.6** (-18%) 0.0493
ADAS-Cog 13	5.162	**-0.701** (-14%) 0.1962	**-1.400** (-27%) 0.0097
ADCS-ADL-MCI	-4.3	**0.7** (-16%) 0.1515	**1.7** (-40%) 0.0006

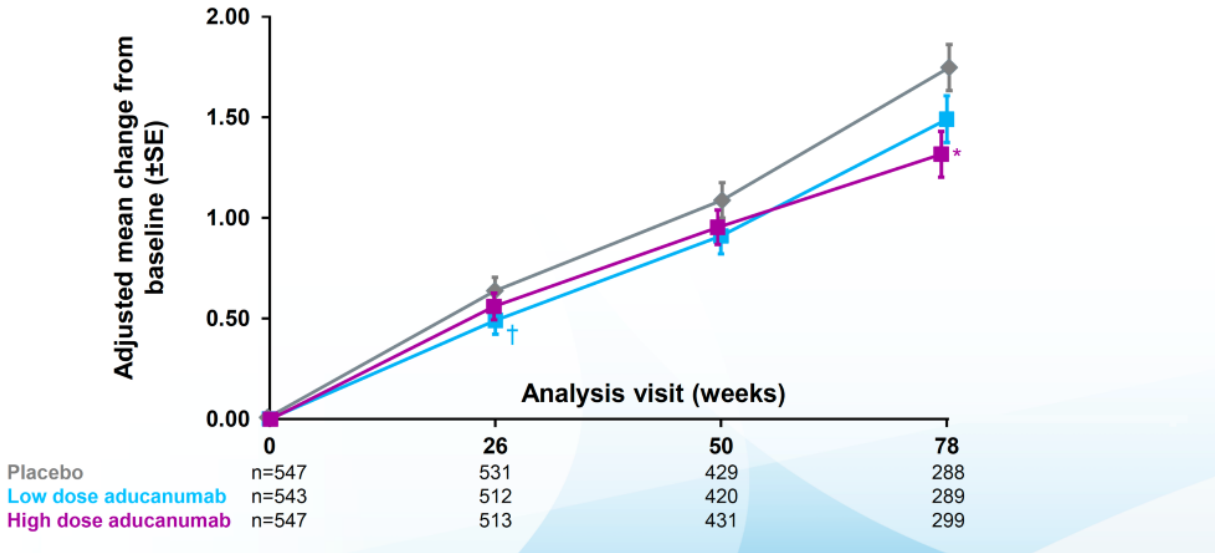
EMERGE and ENGAGE Topline Results: Two Phase 3 Studies to Evaluate Aducanumab in Patients With Early Alzheimer's Disease presented at 12th Annual Clinical Trials on Alzheimer's Disease (CTAD) Meeting, 2019. Budd Haeberlein S. Clinical Trials on Alzheimer's Disease. EMERGE and ENGAGE Topline Results: Two Phase 3 Studies to Evaluate Aducanumab in Patients With Early Alzheimer's Disease, 2019.

Table 2: Link between CDR Domain and Impact on Quality of Life

CDR Domain	QoL Impact
Memory	Memory loss affects QoL by depriving patients of the ability to remember both everyday moments such as where the food is kept to major life events such as their wedding day, children, or grandchildren.
Orientation	It can be completely disorienting to a patient who is unable to accurately track the passage of time. Seconds may blend into days wherein bill payments are forgotten and a spouse's birthday anniversary is missed. A patient's QoL is also severely hindered when there is the potential to get lost when taking a walk in their own neighborhood.
Judgement & Problem Solving	Impaired judgement and problem solving decreases a patient's independence and impacts QoL through increased fear and danger in unfamiliar situations. It may lead to loss of ability to drive or operate household appliances.
Community Affairs	As humans are social creatures, the increasing dearth of social engagement (be it through work, shopping, or social events) takes a toll on a patient's happiness and QoL. They may become lonelier when their connections to the world are slowly stifled.
Home and Hobbies	Hobbies and the ability to maintain a household are critical to ensuring happiness and peace of mind. When the ability to partake in the things that give them joy and provide order to the home are taken away, a patient's QoL suffers.
Personal Care	The ability to dress oneself and maintain personal hygiene is critical to a patient's sense of independence and achievement. Being unable to dress oneself or maintain proper hygiene takes a mental and physical toll on a patient's QoL.

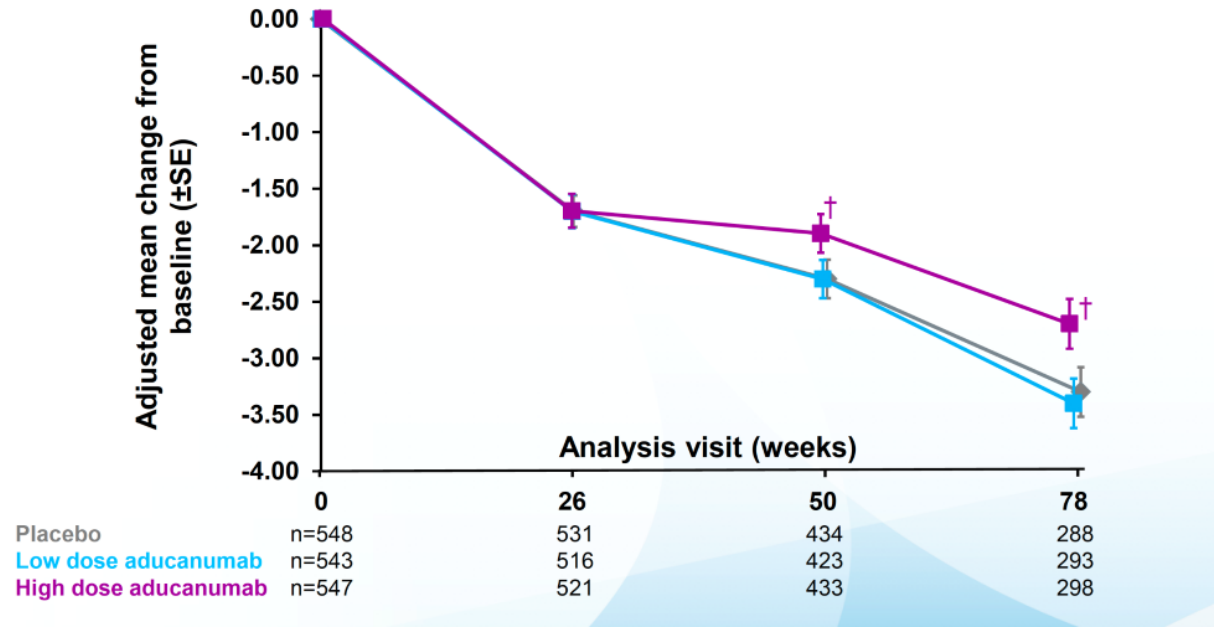
Source: Example CDR Scoring Table. Knight ADRC. Link

Figure 1: EMERGE: Longitudinal change from baseline in CDR-SB



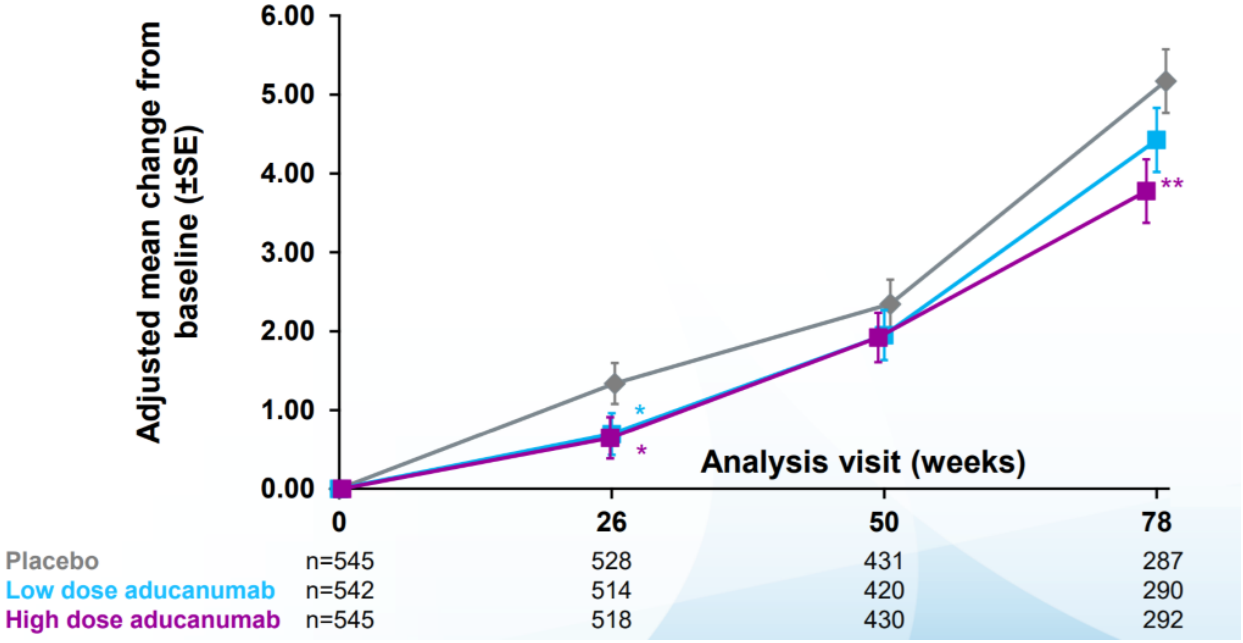
Source: *Op Cit.* Budd Haeberlein *et al.* 2019

Figure 2: EMERGE: Longitudinal change from baseline in MMSE



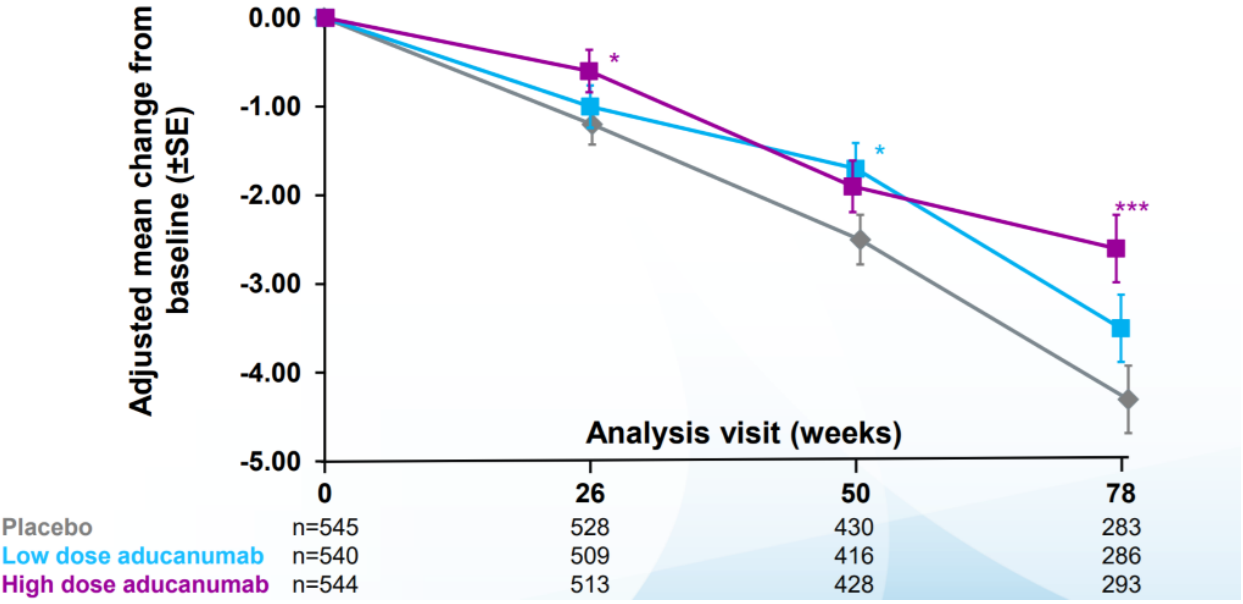
Source: *Op Cit.* Budd Haeberlein *et al.* 2019

Figure 3: EMERGE: Longitudinal change from baseline in ADAS-Cog 13



Source: *Op Cit.* Budd Haeberlein *et al.* 2019

Figure 4: EMERGE: Longitudinal change from baseline in ADCS-ADL-MCI



Source: *Op Cit.* Budd Haeberlein *et al.* 2019

Table 3: Defining the Population for Aducanumab*

Trial Population (MCI due to AD + mild AD dementia) Inclusion Details	
Confirmation of Amyloid Pathology	
Confirmed amyloid pathology through positive amyloid PET scan	
Cognitive Assessment Tool	**Inclusion Criteria**
Clinical Disease Rating (CDR)-Global Score	0.5
Mini-Mental State Exam (MMSE)	Between 24 and 30 (inclusive)
RBANS	≤85

*Details for populations from *EMERGE and ENGAGE Topline Results: Two Phase 3 Studies to Evaluate Aducanumab in Patients With Early Alzheimer's Disease* presented at 12th Annual Clinical Trials on Alzheimer's Disease (CTAD) Meeting, 2019. Note that in the clinical trials, amyloid was confirmed by PET scan, however in the real-world, amyloid confirmation would not be limited to a single diagnostic modality.

Figure 5: The U.S. population of patients with early-stage AD that may benefit from aducanumab is estimated to be 1.4M

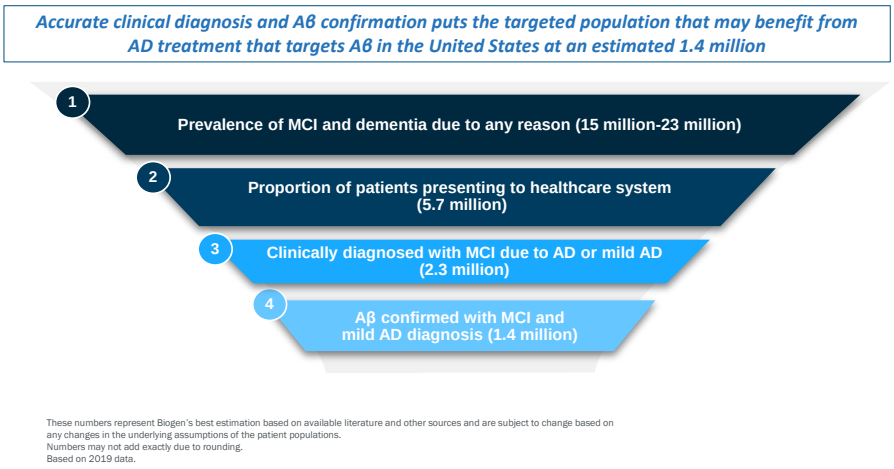
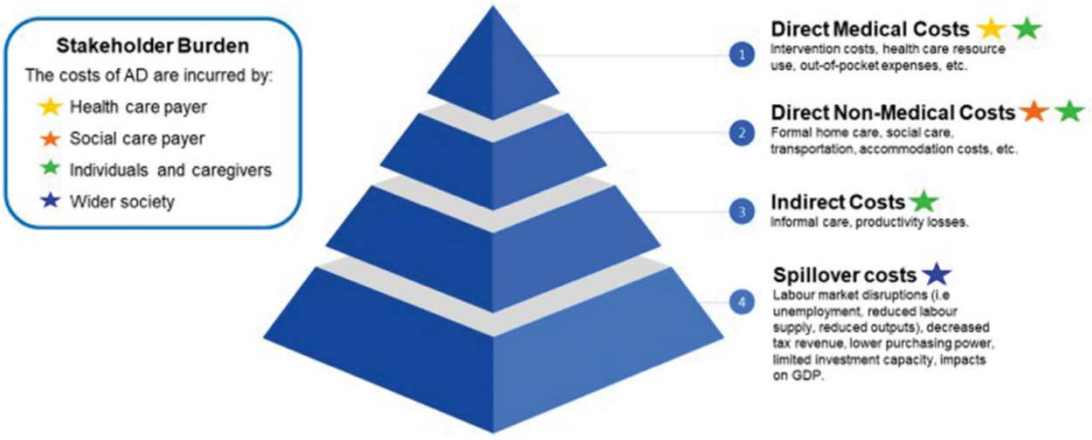
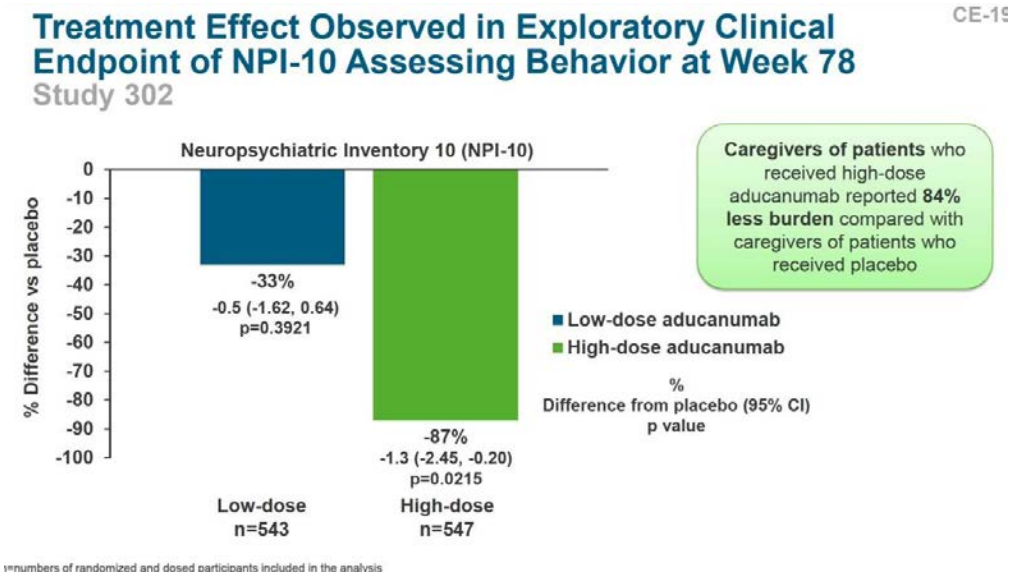


Figure 6: The majority of the economic impact of AD lies outside of the healthcare system



Source: *Op Cit.* Gustavsson. 2020. Link

Figure 7: Caregivers of patients who received high-dose aducanumab reported 84% less burden



Source: US Food & Drug Administration Peripheral and Central Nervous System Drugs Advisory Committee. *Aducanumab for the Treatment of Alzheimer's Disease,* 2020. Link

Genentech
A Member of the Roche Group

November 6, 2020
Institute for Clinical and Economic Review (ICER)
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Boston, MA 02109

Dear ICER Review Panel,

Genentech Inc., a member of the Roche Group, appreciates the opportunity to provide input on the *Aducanumab for Alzheimer's Disease (AD)* Draft Scope [1]. We are dedicated to bringing best-in-class therapies to patients with unmet medical needs through scientific innovation and supporting access to these therapies through patient-centric evidence generation. As part of an ongoing commitment to AD, Genentech is developing gantenerumab, an investigational, monoclonal antibody designed to bind to aggregated amyloid beta and remove amyloid beta plaques. It is currently being investigated in two phase III studies (GRADUATE 1 and 2) for the treatment of early AD.

We provide the following recommendations to more accurately reflect the realities of AD, thereby enhancing the utility and patient-centricity of the report:

1. **Capture a broader range of direct medical costs associated with AD in the health system model by including other forms of direct patient care and assistance costs in addition to "full-time care".**
2. **Adopt a comprehensive approach to modeling caregiver burden in the societal perspective by including family spillover effects.**
3. **Include the proposed societal perspective analysis as a co-base case in the draft report.**

We further expand on these recommendations with supporting rationale and implications below:

1. **Capture a broader range of direct medical costs associated with AD in the health system model by including other forms of direct patient care and assistance costs in addition to "full-time care".**

   Recommendation: Key model inputs should include additional types of patient care utilization (e.g., formal and informal assistance with activities of daily living (ADL) such as nursing homes, assisted living, etc.) incurred prior to a patient requiring "full-time care" or institutionalization.

   Rationale: Alzheimer's disease has a particularly heavy burden on the health care system as patients require increasing caregiver assistance as the disease progresses. The inclusion of delayed entry into institutional care as an outcome and "full time care" as direct medical cost is one critical component of including important patient relevant

outcomes in the planned AD assessment. However, to accurately represent the true direct medical costs associated with AD, the model also needs to include non-institutionalized caregiving costs [2]. In earlier stages of disease progression, caregiving frequently involves in-home assistance with one or more ADLs (e.g., bathing and dressing), as well as multiple instrumental ADLs, such as paying bills, shopping and using transportation [3-5]. This type of formal home health care is estimated to represent up to 20% of total AD direct medical costs [6]. Accurate representation of the medical cost burden for AD patients therefore requires inclusion of costs such as personal care services, home nursing care, assisted living facilities, and specialized dementia care facilities [2,6].

Implications: Accounting for the medical costs associated with all forms of direct patient care and assistance in the health system base-case will ensure the assessment considers the true cost of AD. Ignoring these costs risks underestimating the potential benefits of an "effective" disease modifying therapy (DMT) in AD for healthcare payers, patients, and families.

2. **Adopt a comprehensive approach to modeling caregiver burden in the societal perspective by including family spillover effects.**

Recommendation: The (modified) societal perspective should include family spillover costs (e.g., unpaid informal caregiver time, caregiver productivity, non-medical direct costs, financial vulnerability) and spillover health effects (e.g., caregiver quality of life (QoL), caregiver direct medical costs, wellbeing of a family) to accurately represent the burden of AD.

Rationale: Alzheimer's disease is associated with an immense need for formal and informal caregiving. Friends and family members are estimated to provide almost 75% of caregiving for AD patients [7,8]. When applying the societal perspective, ICER should seek to incorporate all costs and health effects related to AD, which includes impact on family members and impacts outside of the healthcare sector [9,10].

Alzheimer's disease also imposes a significant physical, emotional, and financial toll on family members and informal caregivers. Diagnosis of even early AD leads to financial vulnerability for family members [11,12]. Further, family members and informal caregivers commonly face a cost burden to cover supplemental care and non-direct medical costs (e.g., home modifications, transport to medical appointments) [13-16].

Additionally, family caregivers are at increased risk of health and mental issues, including anxiety, depression and sleep disorders, impacting both caregiver QoL and their own direct medical costs [7,9,17,18]. Thus, it is important to also capture the financial spillover effects to families and caregivers, including impacts on work productivity, consideration of unpaid caregiving, and out-of-pocket direct and indirect costs [7,9,19].

Implications: Incorporating key elements of AD's impact on caregivers and family members in the cost-effectiveness model results, from the time of the draft model report, will allow for a more realistic assessment of a potential DMT on disease burden.

Genentech
A Member of the Roche Group

3. **Include the proposed societal perspective analysis as a co-base case in the draft report.**

   Recommendation: Due to the heavy and well-established burden of AD on patients, families, and society, the modified societal perspective should be presented as a co-base case in the draft evidence report.

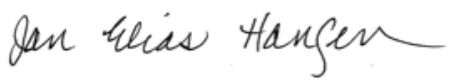
   Rationale: The long duration of the AD disease course before death contributes significantly to the public health impact of AD as much of that time is spent in a state of disability and dependence [3]. Additionally, a review of AD cost-utility analyses found spillover costs were typically incorporated as caregiver time costs, and often significantly affected the findings [9]. Due to the prevalence of AD, its established impact on family and friends, as well as its large and often publicly funded costs, the modified societal perspective should be included as a co-base case.

   Implications: Explicitly including the societal perspective as a co-base case will address patient and caregiver concerns by fully evaluating the burden of AD and potential impact of a DMT.

Conclusion

Society has been waiting with great anticipation for a DMT in AD. This is a critical moment for ICER to conduct an assessment that accurately reflects the significant burden of AD on patients, families, and the health system. The decisions on how comprehensively or narrowly the current burden is defined will have substantial implications on continued innovation. We appreciate the opportunity to comment and hope our recommendations will lead to a more comprehensive evaluation that represents the needs of all stakeholders.

Sincerely,



Jan Elias Hansen, Ph.D.
Vice President, Evidence for Access Medical Unit
Genentech, US Medical Affairs

Genentech
A Member of the Roche Group

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Eli Lilly and Company
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November 9, 2020

RE: Lilly Response to ICER's Draft Scoping Document- Alzheimer's Disease

Alzheimer's disease (AD) has so far presented an intractable challenge to patients, providers, researchers, and society. Individuals with AD lose their memories, their independence, their relationships and, ultimately, their lives. If left unchecked, the number of Americans suffering with AD will more than double by 2050, from 5.8 million to 13.8 million, and annual medical costs will more than double to top $1 trillion. People with AD eventually require round-the-clock care and family caregivers, often pushed to their limits as they care for loved ones, incur additional economic and health care costs of nearly $250 billion in the United States every year. Such costs threaten to overwhelm health budgets for the U.S. and governments around the world. Scientists researching potential treatments to slow down the progression of Alzheimer's have suffered numerous clinical trial failures, and no disease-modifying medicine has yet been approved. The review of aducanumab by the U.S. Food and Drug Administration could, in early 2021, bring the first such treatment to patients.

Like the disease, putting a value on a disease-modifying medicine for AD also presents a major challenge. Traditional approaches to valuing medical interventions are in many ways mismatched with the circumstances of AD impact and care as well as the preferences of people with AD and those caring for them. Also, fragmentation in the way AD care is provided and paid for creates challenges in capturing the impact of the disease and the value of slowing it. Through scientific advancements, we now know that the pathology of AD can appear in the brain 10-20 years before patients experience symptoms. For a variety of reasons, Alzheimer's disease is often not detected early and in many cases a diagnosis is never disclosed to the patient, thus leaving families to face the predictable progression in the form of unnecessary crises and putting additional burden on healthcare utilization and personal financial impact. Tracking the cost and impact of care over such a long time horizon and such a wide range of care settings is more difficult than in perhaps any other disease.

Given these challenges, we support the effort by the Institute for Clinical and Economic Review (ICER) to assess the clinical and economic effectiveness of aducanumab and to create an economic model for tracking its impact over time. We also applaud ICER's efforts to gather and incorporate feedback from a broad range of stakeholders and to consider the value of a potential AD medication from multiple perspectives—including health systems, patients, and their loved ones. ICER has already done significant work to collect the perspective of patients and caregivers, and we applaud ICER on the comprehensive scope and set of value measures

outlined in its draft scoping document. We are encouraged by ICER's stated intention to consider both direct and indirect medical costs holistically from both the health system and societal perspectives and to consider quality of life issues, both those measured traditionally and those identified as important by patients and caregivers.

ICER's work is important because setting an appropriate value for AD therapies and, more broadly, the diagnostics and detection practices necessary for their use, is critical to solving the challenge of Alzheimer's disease. If we appropriately value these interventions and their benefits, we can stimulate the innovation patients are waiting for and accelerate patients' access to the care they and their loved ones so desperately need. Toward those goals, we at Eli Lilly and Company offer the following comments and suggestions.

Clinical Scope

Given the unique nature of aducanumab, we agree with the use of "Best Supportive Care" as the appropriate comparator. This requires that ICER carefully evaluate not only direct medical costs but also a broader set of indirect costs typically not considered in ICER's cost-effectiveness analyses. This should include caregiver direct medical costs as well as their indirect costs (e.g., as could be estimated from Medicare claims). We applaud ICER on the comprehensive scope and set of value measures to be incorporated into the formal cost-effectiveness evaluation. The proposed approach harkens back to the 2015 ICER Value Framework model Version 1[i], where a broader set of value measures were included for the formal assessment of value. We are most encouraged by the broad set of "Patient Outcomes Measures" listed on Pg. 5 of the ICER Draft Scoping Document[ii]. We feel that these are all critical to include in the formal assessment of Clinical Cost-Effectiveness, which impacts ICER's recommendations and evaluation of other issues (e.g., the price of an intervention). While we appreciate the challenge of expanding direct medical costs to caregivers and of obtaining the necessary data and valuing the non-traditional measures in a formal cost-effectiveness analysis, we encourage you to make the effort to value and include these appropriately. It will not only address some of the weakness in a solely QALY-based analysis based on patient costs, but also ensure that the final evaluation and recommendations offer the best evidence on value for all stakeholders. An expanded set of value measures is consistent with the practices recommended by the ISPOR Special Task Force on Value Assessment Frameworks[iii]. While such an evolution may be out of cycle for the current ICER methodology revision cycle, a fair and appropriate evaluation of an AD intervention requires additional measures of value lest the ICER evaluation make the wrong recommendations due to missing and necessary elements of value. This is the first of several issues where a flawed analysis could have an adverse impact on patients and caregivers.

Potential Other Benefits and Contextual Considerations

Given our previous comments, we are concerned that many important issues will not be adequately addressed in the criteria proposed for the domains of "Potential Other Benefits" and "Contextual Considerations." Take for example the first category of criteria listed, "Uncertainty or overly unfavorable model assumptions creates significant risk that base-case cost-effectiveness estimates are too pessimistic." This is a critical issue and is not one that should be embedded in domains used to adjust the cost-effectiveness threshold. It should be used as a guiding principle in the perspective used as well as what is included in the formal Clinical Cost Effectiveness model. If there is a strong concern that there is significant risk in the model, then it should not be used till the uncertainty is addressed. Our recommendations are intended to help

eliminate such significant risk and bias as concerns. Not sufficiently addressing the risk will result in a biased analysis with flawed recommendations. Using the multiplier correction factors for these domains specified in the ICER methods will not be adequately correct for results from a flawed model.

We also take exception to the measure of "Health Loss" based solely on the QALY. While the QALY may be necessary, it is unlikely to be sufficient and is most likely to be significantly flawed, especially in this disease. This is because the common measures of Quality of Life (QOL), for example the EQ-5D, do not adequately capture the QOL gained or lost in the AD population and their caregivers. The question ICER must answer in assessing these domains is, "What matters most?" Health-loss is diverse and should not be restricted solely to QALY-based health loss. There are many more measures of gain and loss that matter to patients and caregivers. The USAgainstAlzheimer's collaborative did a study to determine what matters most to patients and caregivers. They identified 42 measures that were deemed as distinct and important to patients and caregivers[iv]. Some examples are: "Can complete basic household chores", "takes medications correctly" and "Wash, dress and clothe yourself," which represent the ability to function independently. These represent more meaningful measures of loss, and while these represent a challenge to quantify, it is feasible to do so. The assessment of these two domains deserves a thorough vetting based on what is important to society, patients, and caregivers, and not a simple reliance on past efforts used in other settings and therapeutic areas (e.g., sole use of the QALY). A failure of ICER not to be more comprehensive will result in a flawed evaluation that does not capture many feasible and necessary measures of benefit to AD patients and their caregivers.

Scope of Comparative Value Analyses

The scoping document indicates that the health system perspective, and not the societal perspective, will guide the ICER Clinical Cost-effectiveness evaluation—both in its model structure and content. Based our above comments, we feel that this is a mistake and recommend that the societal perspective be given equal consideration in determining which measures are used in the cost-effectiveness model and the subsequent recommendation on the overall value and pricing of an AD intervention. Considering ICER has chosen "Best Supportive Care" as the comparator, the use of the health system perspective alone will exclude many relevant measures of clinical and economic value; this will result in a biased and unfair evaluation of the more costly medical interventions. Using only the more limited health system perspective will have a significant negative impact on the final recommendations as well as on society and patients and their support network (e.g., caregivers).

Low Value Care

We commend ICER on the inclusion of this important factor in value assessment. It should lead ICER to consider the wasted care that occurs to due to missed diagnoses and misdiagnoses. While the assessment of diagnostic technology is outside of the scope of the ICER evaluation, there is significant data on the nature and economic benefit of an early and accurate diagnosis[v]. The advantages and cost avoidance of appropriate and timely diagnosis should be considered as an important factor in ICER's Low Value Care as well as when assessing potential savings or cost-offsets to the health systems and families as part of the overall management and treatment of AD patients.

Conclusion

Again, we at Eli Lilly and Company applaud ICER's attention to the complexities of valuing therapies for Alzheimer's disease, as well as ICER's openness to input from other organizations on how to manage those complexities. We hope our comments contribute to a productive discussion and to further refinement of ICER's approach. We would welcome any follow-up questions or discussions.

Sincerely,

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Submitted via email: publiccomments@icer-review.org

RE: Response to ICER Scoping Document for Comparative Clinical Effectiveness and Value Assessment of Aducanumab (Biogen) for Treatment of Alzheimer's Disease

Dear Colleagues,

This letter is being submitted by UsAgainstAlzheimer's (UsA2) in response to ICER's Draft Scoping Document released on October 21, 2020, intended to frame its assessment of the comparative clinical effectiveness and value of aducanumab. UsA2 is a patient-driven, non-profit organization that exists to conquer Alzheimer's disease (Alzheimer's). Driven by the suffering of millions of families, UsA2 presses for greater urgency from government, industry and the scientific community in the quest to end Alzheimer's disease and related dementias (ADRD).

Our comments in this letter are focused on factors that should inform how you will approach your task to evaluate the health and economic outcomes of aducanumab for AD. As you note:

> "the ICER Value Framework includes both quantitative and qualitative comparisons across treatments to ensure that the full range of benefits and harms—including those not typically captured in the clinical evidence such as innovation, public health effects, reduction in disparities, and unmet medical needs—are considered in the judgments about the clinical and economic value of the interventions."

UsA2 believes that the impact of the work that ICER has elected to undertake has dimensions that far exceed the determination of value for this single product. This is the first time that a formal process has been undertaken to examine the value of a prospective disease-modifying therapy in Alzheimer's. This process will set the course for how our nation listens to the voices of those affected by Alzheimer's – both patients and caregivers – to understand what outcomes are clinically meaningful in their eyes, as opposed to those that are clinically measurable in the context of a clinical trial. Finally, given the unique societal burden of Alzheimer's – a disease which has economic impacts at the individual, household and societal level – this decision holds the potential for impact on our nation's fiscal health and security.

We offer the following comments with this in mind and we look forward to continued dialog throughout the process.

I. Components of Scoping Document that we support

ICER offers a solid overview of the background against which this review is being undertaken. You have recognized key surrounding contextual issues, specifically the underdiagnosis of AD, the lack of cohesive care after diagnosis, outcomes other than cognition and function that are important to patients and their caregivers, and the impact of AD on the caregiver. UsA2 wishes to underscore the importance of recognizing core outcomes that may not be captured in commonly deployed primary and secondary endpoints in today's clinical trials. We endorse ICER's recognition that:

> "The main goal of patients and caregivers is to prolong the time the patient remains independent, rather than prolonging length of life, and they are eager for treatments that will help the patient remain independent and delay the need for around-the-clock care. Furthermore, in addition to cognition and function, patients ranked emotional stability and wellbeing, preventing a "loss of self," becoming a burden on their families and caregivers, and safety as important outcomes to consider."

We emphasize that the transition from independence to the need for around-the-clock care is gradual with many intermediate outcomes that require assessment.

Further we underscore here and discuss below how this review should factor in the impact on Caregivers. Again, we support your findings:

> "The impact of AD on caregivers is substantial. Nearly half of all caregivers who provide care to older adults do so for someone with AD or dementia, with women not only more likely to be caregivers but also to spend more time providing care than men. As the disease progresses to moderate-to severe dementia and the patient loses function, caregivers take on a greater physical and emotional load. As a result, there may be physical and mental health consequences for the caregivers themselves such as increased chronic health conditions, depression and isolation, and increased use of the health care system."

However, the final sentence should not present this finding as speculative. There are significant and well documented physical and mental health consequences for an Alzheimer's caregiver, and they must be central to this assessment.

Regarding ICER's statement of outcomes, we support the listing and the inclusion of "other outcomes" you mention, specifically those on "Caregiver Impact, to include, Caregiver quality of life; Caregiver health and associated costs; Caregiver productivity." These caregiver impacts must be included in the base-case model scenario and retained as important outcomes in the overall Assessment.

Further, we stress the need to understand how even a modest change in a primary, secondary or even tertiary endpoint in the aducanumab clinical trial may be linked to outcomes that are rated as most important by patients and caregivers surveyed in the Alzheimer's Disease Patient and Caregiver Engagement (AD PACE) What Matters Most Study. Patients and caregivers have identified and rated 42 concepts of interest that matter most to them. As discussed, we will provide a full view into the WMM Study through a separate data sharing arrangement with ICER.

Finally, your introduction mentions that this assessment will capture "the full range of benefits and harms—including those not typically captured in the clinical evidence such as innovation, public health effects, reduction in disparities, and unmet medical needs." Each of the underscored points (our emphasis) is key here.

In terms of innovation, having access to a first-in-class disease-modifying therapy is a critical step to moving toward best-in-class treatments, as has been seen with oncology, HIV-AIDS, and rheumatology. Your assessment should be undertaken as part of the ecosystem that heralds and supports innovation that is safe and effective, moving key decisions into the hands of patients and physicians to weigh whether the potential benefit of the therapy is right for a particular patient given that patient's risk tolerance profile. ICER should be flexible in your determination of value as a first-ever treatment will help ensure ongoing

innovation to create competition and best-in-class products that eventually reduce the overall cost while improving outcomes.

Regarding public health impact, we discuss below the potential health benefits for caregivers, individuals who may be spouses, children, other family members. By delaying progression, an intervention such as aducanumab minimizes this expanding and often-underreported burden on caregivers as part of our nation's public health system.

In terms of health disparities, as noted in our prior communication, the Alzheimer's journey delivers grave, disproportionate impacts on communities of color and people who have low income and wealth. This disease is more prevalent with greater human and financial impacts sustained across these communities, greater dependence on Medicaid, and fewer self-pay resources. Equitable access to new therapies will have substantial, concomitant reduction in the Alzheimer's health disparities.

II. Concerns

UsA2 has several concerns with definition and valuation of 'best supportive care' as the working comparator.

A. **First, we ask ICER to clarify the "best" portion of "best supportive care" proposed as the reference AD intervention**. Although we too want the best care for all people with AD, the word "best" does not appear in the ICER descriptions of interventions for other diseases, nor is it defined in the background and scope description. We would like clarification as to what it means and why it appears solely in the context of AD.

B. **We ask ICER to evaluate and include the costs of all compensated and uncompensated supportive care, whether part or full time, in its AD cost estimates of "best supportive care."** We appreciate that ICER recognizes that supportive care is the current standard of care for AD. The majority of supportive care is provided on an uncompensated basis by family and friends of the patient before and, often even after, an individual reaches the key outcome of full progression and requires "full-time care." Yet, per the scope description, it is unclear if ICER has considered the value of the uncompensated supportive care provided by the family and friends, or if you intend to include in caregiver impacts or other indirect costs[1] . Furthermore, the scope description is not clear whether even the compensated supportive care provided in community and institutional settings is included in care costs. Compensated supportive care includes care paid for by patients and families, Medicaid, and long-term care insurance. It is critical that the scope considers these costs and impacts.

   The Health and Retirement Study (HRS) reports that in 2010 the average cost of dementia care was $27,789 for informal (family and friends) home care valued according to replacement cost and $28,501 for care purchased in the marketplace.[2] Supportive care represented all the informal care and the vast majority of care purchased in the marketplace.

   The burden of family and friend care falls disproportionately on people whose labors society has most often undervalued and marginalized: women, people of color, and the

[1] Per the Scope of Comparative Value Analyses section of the Draft Background and Scope document, productivity impacts are to be included as an indirect cost in the societal impact scenario analysis, "data permitting".
[2] Hurd, "Monetary Costs of Dementia in the United States", NEJM, 2013.

elderly. Assigning no value to their work would be both economically incorrect and socially unjust. All work has value and is ultimately "paid for" by someone. Uncompensated family and friend caregiving labor has opportunity cost value even when it does not displace (paid) work productivity. If not for Alzheimer's disease care, uncompensated family and friend caregivers could be enjoying a better financial situation, better personal health, less heartbreak, and a better total quality of life. The "stay at home" daughter could be working outside the home if not for the burden of Alzheimer's disease. The "retired" spouse could instead be caring for grandchildren and contributing to the wealth of the next generation or simply enjoying the fruits of decades of labor. Furthermore, many caregivers juggle the double burden of uncompensated caregiving and paid employment. At the very least, family and friend care should be valued at Medicaid's hourly cost for such services, irrespective of whether the care is paid for by Medicaid.[3]

C. **We ask ICER to include the cost of community and institutional supportive care (part-time and full-time care) described in II. B. as a direct healthcare cost in the base case scenario analysis.**

When the standard of care for a disease is supportive care, the cost of supportive care is a direct cost. Caregiving is no less a direct cost of Alzheimer's disease than dialysis is a cost of renal disease or insulin is a cost of diabetes. The cost of caregiving therefore must be included in the healthcare costs of Alzheimer's disease, on par with hospital, physician, and drug costs.

We agree that caregiver paid-work productivity losses (the value of lost paid-work productivity in excess of the value assigned to caregiving) should be assessed as part of societal costs.

D. **We ask ICER to clarify inclusion of supportive care in its evaluation framework**.

As stated above, we believe that inclusion of the full value of supportive care is essential to any primary analysis of AD and would like a framework clarification that supports our position. The ICER framework currently states that ICER's primary analytic perspective is "the health care system" and implies that the boundaries of the health care system are defined by what is paid-for via private and public health insurance plans.[4] Supportive care is sometimes covered and sometimes not covered by private and public health insurance plans, without clear enunciation of boundaries. Supportive care is often paid-for by private and public health insurance payers when the support is provided in conjunction with non-supportive medical services. For example, payers pay the entire inpatient hospital bill and do not exclude the room and board (supportive care) portion of the bill. Payers also pay for supportive nursing home care following inpatient care. Furthermore, Medicaid and long-term care insurance routinely pay for supportive care as a stand-alone service.

Some might argue that "paid-for by health insurance payers" is itself the boundary between costs that should and should not be included as a health care system cost. If so, it's a

[3] Family and friend care is sometimes compensated by Medicaid as a self-directed home and community-based service (HCBS): https://www.medicaid.gov/medicaid/home-community-based-services/home-community-based-services-authorities/self-directed-personal-assistant-services-1915-j/index.html.

[4] ICER, "2020-2023 Value Assessment Framework", page 24.

capricious boundary. A patient's income and assets determine whether Medicaid pays for supportive care services. As recently as 2005 Medicare did not cover prescription drugs. Yet, for sure, if the clock was rolled back, ICER surely would not omit the prescription drug costs of Medicare beneficiaries from a value assessment if conducted pre-2006.

UsA2 has several concerns related to quality of life and health states.

E. **We are concerned that ICER's modeling decrements may not capture the gradients of the AD patient's experience and hence costs and quality of life. If so, we ask that ICER include intermediate care decrements.** There are multiple references in the scope description that *suggest* (not confirm) that ICER plans to primarily differentiate between people with AD as those who need full-time supportive care and those who don't need full-time supportive care and are, in ICER's terminology, "independent." Furthermore, there seems to be additional intent to further divide those who need full-time supportive care between the institutionalized and the non-institutionalized. Yet, the majority of people with AD and especially those who will be benefited by aducanumab are on the spectrum "semi-independent," meaning that they need less than 24x7 supportive care but are not fully independent. We ask that ICER assure the costs of meeting such patients' "intermediate" support needs and their quality of life are included in the modeling.

F. **Since quality of life is <u>the</u> central concern of AD patients and caregivers, we would like to review and comment upon the source evidence ICER plans for determination of patient quality of life values and assigning the weights necessary to convert quality of life to QALYs**. The Draft Background and Scope document, however, provides no specific information concerning ICER's plan.

G. **We suggest that ICER consider assigning a negative health utility to the most advanced stage of AD**. While health utilities are most often expressed on 0.00 to 1.00 scale, where 1.00 is perfect health and 0.00 is death, the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) and other economics groups/economists allow for the possibility of assigning negative health utility to health states deemed "worse than death".[5] Our work with AD patients and caregivers confirms that many patients and caregivers consider the most disabling stage of advanced Alzheimer's, where the patient has no cognition and is fully dependent, to be a health state worse than death.

H. **Since changes in the level of a patient's health state, which are directly linked to the level of supportive care, are key to evaluating the cost effectiveness of aducanumab therapy, we would like to review and comment upon ICER's plan for converting the aducanumab trial outcomes to specific health states.** The Draft Background and Scope document provides no specific information concerning ICER's plan.

Finally, UsA2 has concerns related to the co-based societal perspective and the presentation thereof.

[5] ISPOR, "Estimating Health-State Utility for Economic Models in Clinical Studies: An ISPOR Good Research Practices Task Force Report", Value in Health, 2016.

I. **We ask that the co-base societal perspective scenario analysis be included alongside each report of the base-case analysis.** We appreciate that ICER's framework includes the possibility of a societal perspective scenario analysis as "co-base case".[6] The societal perspective is particularly important for AD, and we ask that the results of the societal analysis be give parity with the primary analysis and not be relegated to a different section of the report – in other words displayed as a true "co-base".

J. **We urge ICER to include the family-caregiver's incremental health care costs and QALYs in the co-base societal perspective scenario analysis.** A family-caregiver's health and quality of life is adversely impacted by the progression of the AD patient's care needs, even if the caregiving is paid (such as by Medicaid). Providing supportive care is much more depleting than a typical job and is not a job that they can quit. The incremental healthcare costs that caregivers experience should be included in the cost (numerator) portion of the societal analysis and incremental caregiver QALYs should be included in the QALY (denominator) portion of the analysis. While the background portion of the Background and Scope document suggests the possibility of inclusion, the scope description does not confirm ICER's intent.

III. Conclusion

We appreciate the complexity of the analytical work ahead and want to be as helpful as possible to your work. In this regard, we would like to submit further evidentiary resources that are supportive of our comments and ask that you confirm your willingness to receive these.

We look forward to speaking with your team soon.

Sincerely,

Russ Paulsen
Chief Operating Officer
UsAgainstAlzheimer's

[6] Draft Background and Scope document, page 7