Aducanumab for Alzheimer's Disease: Effectiveness and Value

Final Evidence Report and Meeting Summary

August 5, 2021

Prepared for

January 17, 2023 Update: Per ICER's guidelines on the acceptance and use of "In-Confidence" data from manufacturers of pharmaceutical products, academic-in-confidence data that was redacted in the report has been unmasked 18 months following the ICER Public Meeting date.

January 12, 2023 Update: Due to an editing error, the graph titles in Figure 3.3 were labeled incorrectly. The titles have been updated to accurately reflect the data in the graphs.

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Grace A. Lin served as the lead author for the report. Patricia G. Synnott led the systematic review and authorship of the comparative clinical effectiveness section in collaboration with Avery McKenna and Emily Nhan. Melanie D. Whittington was responsible for the development of the cost-effectiveness model. Jon Campbell provided oversight of the cost-effectiveness analyses and

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About ICER

The Institute for Clinical and Economic Review (ICER) is an independent non-profit research organization that evaluates medical evidence and convenes public deliberative bodies to help stakeholders interpret and apply evidence to improve patient outcomes and control costs. Through all its work, ICER seeks to help create a future in which collaborative efforts to move evidence into action provide the foundation for a more effective, efficient, and just health care system. More information about ICER is available at https://icer.org/.

The funding for this report comes from government grants and non-profit foundations, with the largest single funder being the Arnold Ventures. No funding for this work comes from health insurers, pharmacy benefit managers, or life science companies. ICER receives approximately 29% of its overall revenue from these health industry organizations to run a separate Policy Summit program, with funding approximately equally split between insurers/PBMs and life science companies. Life science companies relevant to this review who participate in this program include Biogen. For a complete list of funders and for more information on ICER's support, please visit https://icer.org/who-we-are/independent-funding/

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In the development of this report, ICER's researchers consulted with several clinical experts, patients, manufacturers, and other stakeholders. The following experts provided input that helped guide the ICER team as we shaped our scope and report. It is possible that expert reviewers may not have had the opportunity to review all portions of this report. None of these individuals is responsible for the final contents of this report, nor should it be assumed that they support any part of it. The report should be viewed as attributable solely to the ICER team and its affiliated researchers.

For a complete list of stakeholders from whom we requested input, please visit: http://icerorg.wpengine.com/wp-content/uploads/2020/10/ICER_AD_Stakeholder_List_111820-1.pdf

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In addition, Peter J. Neumann has served on several health economic advisory boards and consulted with various pharmaceutical companies, including Biogen.

Alzheimer's Association Review Panel

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 www.alz.org/transparency.

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Report Supplement

List of Acronyms and Abbreviations Used in this Report

AD	Alzheimer's disease
ADAS-Cog 13	Alzheimer's Disease Assessment Scale – Cognitive Subscale
ADSC-ADL-MCI	Alzheimer's Disease Cooperative Study – Activities of Daily Living Inventory
AE	Adverse event
AHRQ	Agency for Healthcare Research and Quality
APOE ε4	Apolipoprotein ε 4
ARIA[-E,H]	Amyloid-related imaging abnormalities[-edema/effusion, hemorrhage or superficial siderosis]
CDR-SB	Clinical Dementia Rating Scale – Sum of Boxes
CI	Confidence interval
CSF	Cerebrospinal fluid
evLYG	Equal value of life years gained
FDA	Food and Drug Administration
HBPB	Health benefit price benchmark
HR	Hazard ratio
HRQoL	Health-related quality of life
ICER	Institute for Clinical and Economic Review
ITT	Intention-to-treat
IV	Intravenous
kg	Kilogram
LTC	Long-term care
LY	Life year
MCI	Mild cognitive impairment
mg	Milligram
MMSE	Mini-Mental State Exam
MRI	Magnetic resonance imaging
N	Total number
n	Number
NICE	National Institute for Health and Care Excellence
NPI-10	Neuropsychiatric Inventory 10
NR	Not reported
PET	Positron emission tomography
PICOTS	Population, Intervention, Comparators, Outcomes, Timing, Settings
PV4	Protocol Version 4
QALY	Quality-adjusted life year
SD	Standard deviation
SE	Standard error
SUVR	Standardized uptake value ratio
US	United States
WAC	Wholesale acquisition cost

Executive Summary

Alzheimer's disease (AD) is a fatal neurodegenerative brain disease characterized by the progressive accumulation of beta-amyloid protein plaques and neurofibrillary tangles; these are hypothesized to damage neurons and lead to the loss of cognition and physical functioning.[1] AD affects almost six million people in the United States (US), with more women than men affected and Black Americans at a higher risk of developing the disease.[2] Symptoms of AD include impairment of memory, language, executive function, and visuospatial function that affects one's ability to function. Other symptoms include changes in mood or personality and sleep disturbances. Eventually, patients may require around-the-clock in-home or institutional care. The average life expectancy of patients with AD is four to eight years.[2] As the disease progresses, caregiver impact—most often done by unpaid family members and friends—increases significantly. Caregivers can suffer significant negative physical, financial, and emotional outcomes from the strain of caregiving.[3,4]

Current treatment of AD is focused on supportive care, which may include treatment of dementia symptoms with medications that do not alter the course of the disease.[5,6] Because of the devastating burden of AD, there is a great need for disease-modifying treatments that slow or stop progression of the disease. Aducanumab ("aducanumab-avwa"; Aduhelm™, Biogen), a human monoclonal antibody that promotes clearance of beta-amyloid plaques from the brain, is a potentially disease-modifying treatment that was granted accelerated approval by the US Food and Drug Administration (FDA) on June 7, 2021 for patients with AD. It is given as an intravenous (IV) infusion every four weeks.

Aducanumab was evaluated in two identical, mostly contemporaneous Phase III randomized clinical trials (RCTs), ENGAGE and EMERGE. The trials randomized patients with early AD (i.e., mild cognitive impairment [MCI] or mild dementia due to AD) to low- or high-dose aducanumab or placebo (exact dosing depended on the presence or absence of a genetic marker of AD risk, apolipoprotein ε4 [APOE ε4]). In both trials and at all doses, aducanumab effectively removed beta-amyloid. The primary clinical outcome was change in mean score on the Clinical Dementia Rating Scale – Sum of Boxes (CDR-SB). Midway through the trials, the trial protocol was amended such that the high-dose group was titrated to 10 mg/kg, regardless of APOE ε4 status (post-Protocol Version 4 [PV4]). In March 2019, ENGAGE and EMERGE were terminated following a prespecified interim analysis for futility. Subsequent analyses revealed a possible positive treatment effect from EMERGE (Table ES1), though a minimal clinically important difference in CDR-SB has not been clearly defined. However, results from ENGAGE failed to detect any improvement in CDR-SB in the high-dose group compared with placebo. Analyses of secondary endpoints were consistent with the primary endpoint result in each trial (positive in EMERGE, negative in ENGAGE).

The manufacturer explored possible explanations for the discordant results between the two trials; they concluded that the timing of PV4 allowed more patients in EMERGE than ENGAGE to receive

the full high-dose regimen (28.8% vs. 22.3%) and that randomization had failed to balance "rapid progressors" in ENGAGE.

Table ES1. Change in CDR-SB Compared with Placebo According to Analysis Method

Clinical Trial	Low-Dose Aducanumab*	High-Dose Aducanumab*
ITT Population		
ENGAGE (n=1647)	-0.18 (-0.47, 0.11)	0.03 (-0.26, 0.33)
EMERGE (n=1638)	-0.26 (-0.57, 0.04)	-0.39 (-0.69, -0.09)†
Summary Estimate from Meta-Analysis	*-0.21 (-0.43, 0.00)*	*-0.18 (-0.60, 0.24)*
Post-Hoc Analysis Opportunity-to-Complete Population‡		
ENGAGE (n=956)	-0.12	0.08
EMERGE (n=981)	-0.27	-0.36†
Post-Hoc Analysis Post-PV4 Population		
ENGAGE (n=790)	-0.35 (-0.88, 0.18)	-0.48 (-1.02, 0.06)
EMERGE (n=887)	-0.42 (-0.94, 0.10)	-0.53 (-1.05, -0.02)†
Summary Estimate from Meta-Analysis	*-0.39 (-0.76, -0.01)†*	*-0.51 (-0.88, -0.13)†*

ITT: intention-to-treat, kg: kilogram, mg: milligram, N/A: not applicable, PV4: Protocol Version 4

*The initial dosage of aducanumab was based on APOE $\varepsilon 4$ status. APOE $\varepsilon 4$+ patients were titrated to 3 mg/kg in the low-dose group and 6 mg/kg in the high-dose group; APOE $\varepsilon 4$- patients were titrated to 6 mg/kg in the low-dose group and 10 mg/kg in the high-dose group (ITT population). After PV4 was implemented, APOE $\varepsilon 4$+ patients were titrated to the same dosage as APOE $\varepsilon 4$- patients (Post-PV4 group).

†p<0.05.

‡Opportunity-to-complete population: participants in the ITT population who had the opportunity to complete the week 78 visit by March 20, 2019.

Pooled safety data from the two trials showed that about 35% of patients on aducanumab experienced amyloid-related imaging abnormalities (ARIA), whose clinical effects can range from asymptomatic to severe. Although the majority of patients were asymptomatic or had symptoms such as headache, confusion, or dizziness that resolved with temporary stoppage of the drug, 6.2% of participants receiving the high dose of aducanumab discontinued the drug due to ARIA. Furthermore, some patients experienced bleeding into brain tissue; one death in the Phase Ib trial was attributed to this.

We believe it is possible that ENGAGE and EMERGE found different results because of the explanations put forward by the manufacturer related to rapid progressors and exposure to full-dose therapy; however, other explanations are equally or more likely. The post-hoc analyses do not consistently explain what was seen in the low- and high-dose arms of the trials, and one alternative explanation is that the differences between the trials are due to chance. Furthermore, there is disagreement about whether the degree of improvement seen in EMERGE is clinically important, and the relationship between clearance of beta-amyloid in the brain and clinical improvement has yet to be conclusively demonstrated, with negative results from more than 20 other trials of anti-amyloid drugs. Additionally, aducanumab can cause symptomatic ARIA. Given the certainty that harms can occur in patients treated with aducanumab and uncertainty about benefits, we rate the

evidence to be *insufficient* to determine the net health benefit of aducanumab ("I") in patients with MCI and mild AD. Although clinical trials for aducanumab did not include patients with moderate or severe AD, prior clinical trials of anti-amyloid drugs have suggested a lack of benefit in this population, and thus the potential that aducanumab would benefit patients with severe forms of AD is even less likely.

We estimated the cost effectiveness of aducanumab in addition to supportive care as compared to supportive care alone, assuming blended efficacy from ENGAGE and EMERGE. Base-case results were calculated from both the health care system perspective and the modified societal perspective. The base-case cost-effectiveness threshold prices for aducanumab ranged from an annual price of $2,950 to $8,360 (Table ES2).

Table ES2. Base-Case Annual Cost-Effectiveness Threshold Pricing for Aducanumab

Health Care System Perspective	Annual Price*	Annual Price at $100,000 Threshold	Annual Price at $150,000 Threshold
QALYs Gained	$56,000	$2,950	$5,110
evLYG	$56,000	$4,260	$7,090
Modified Societal Perspective	**Annual Price***	**Annual Price at $100,000 Threshold**	**Annual Price at $150,000 Threshold**
QALYs Gained	$56,000	$3,740	$5,960
evLYG	$56,000	$5,330	$8,360

evLYG: equal value of life years gained, QALY: quality-adjusted life year

*The prices presented in this table are not inclusive of the 6% mark-up. The model adds a 6% mark-up to these annual prices.

In summary, we judge that the evidence is *insufficient* to conclude that the clinical benefits of aducanumab outweigh its harms or, indeed, that it reduces progression of AD in patients with MCI and mild AD. If blended efficacy results are used from the Phase III trials, our base-case analyses suggest that proposed pricing for aducanumab as has been stated by the manufacturer would not be in alignment with its clinical benefits. If aducanumab were determined to have no net health benefit, no threshold price could be generated to guide considerations of fair pricing.

In the health care system perspective, approximately 2.5%, or 35,000 out of 1.4 million AD patients eligible for treatment with aducanumab could be treated within five years before crossing the ICER potential budget impact threshold of $819 million per year. When taking a modified societal perspective, approximately 2.6% of the 1.4 million patients eligible for the treatment with aducanumab could be treated, which equates to roughly 36,000 individuals. Testimony from clinical experts at the public meeting suggested a wide range of clinical uptake of aducanumab, with the majority suggesting numbers well above 100,000 patients over five years. According to our analyses and given that efforts to reach this clinical target would create a short-term potential

budget impact that exceeds ICER's threshold, ICER is issuing an access and affordability alert for aducanumab.

Appraisal committee votes on questions of comparative effectiveness and value, along with key policy recommendations regarding pricing, access, and future research are included in the main report; several key themes are highlighted below.

- To prevent patients and families from being misled, patient groups, the manufacturer, and clinicians should accurately characterize the potential benefits of aducanumab as a slowing of decline of cognition and function and avoid using terms such as "improvement" or "return of quality of life" in all personal statements and advertising.

- Whether aducanumab is widely prescribed or not, health systems, manufacturers, payers, and the FDA should take steps now that will reduce disparities and improve equitable access to dementia diagnosis, management, and future new therapies.

- For AD, the FDA should act quickly to set a clearer regulatory framework in place by specifying a threshold range for amyloid clearance that will be accepted going forward as "reasonably likely" to provide patient benefit. More broadly, the FDA should take concrete steps to become clearer about the way it engages its advisory committees and to be transparent and consistent in its designation of surrogate outcomes and the timing of its decisions to use the accelerated approval pathway.

- Clinicians and clinical specialty societies should bear witness to the unmet needs of patients and families with AD to support broad consideration of the value of emerging therapies. But all clinicians and specialty societies should also exercise their obligation to provide objective guidance on interpreting the uncertain data on aducanumab, and should advocate for fair pricing and for affordable and equitable access to all available treatments.

1. Background

Alzheimer's disease (AD) is a fatal degenerative brain disease characterized by progressive loss of memory, cognitive skills such as language and problem-solving, and physical function. It is the most common cause of dementia in the United States (US), accounting for up to 80% of all dementia diagnoses, and is now the sixth leading cause of death.[2] AD affects an estimated 6.2 million Americans ages 65 years and older and, with the aging population in the US, by 2050, the number of people living with AD is projected to more than double.[2] Two-thirds of those diagnosed with AD are women. There are also racial and ethnic differences in the incidence and prevalence of AD, with higher rates noted in Black Americans and Hispanic populations compared with White and Asian populations (see Supplement A1 for more detailed information).[2,7] Direct and indirect costs of health care related to AD are estimated to be more than $600 billion annually,[8,9] although this may be an underestimate since some non-medical costs (e.g., home safety modifications, adult day care services, adverse effects on caregiver health and productivity) may not be included in cost estimates.

The hallmark of AD is the progressive accumulation of plaques that contain beta-amyloid protein and neurofibrillary tangles of phosphorylated tau protein in the brain;[1] these are hypothesized to set off a cascade that leads to the damage and death of neurons over decades (see Supplement A2 for a more detailed discussion of pathophysiology). However, the exact pathways by which this happens are not fully known. There are different forms of amyloid such as plaques, oligomers, and monomers, and the roles of these different forms and how specifically they are pathophysiologically associated with AD is not well understood. Single-gene mutations that impact beta-amyloid formation (e.g., APP, PSEN1, PSEN2) are associated with early-onset AD. Genetic variants such as the apolipoprotein ε4 (APOE ε4) allele increase one's risk of developing late-onset AD; having one copy of the gene is associated with a two-to-threefold increase in developing AD, while two copies of the gene may increase risk of AD by as much as 15 times.[10] The course of AD can be described in three phases: preclinical disease, mild cognitive impairment (MCI) due to AD, and Alzheimer's dementia. Patients begin to accumulate beta-amyloid in the brain in the preclinical phase up to 15 years prior to the onset of symptoms.[11] Additionally, changes in certain biomarkers in the cerebrospinal fluid (CSF) (e.g., decreased beta-amyloid and increased CSF tau protein levels) and on imaging (e.g., amyloid on positron emission tomography [PET] scans) may occur; such CSF and imaging biomarkers can be used to differentiate AD from other dementias. Once there is a reduction in cognitive function, MCI is diagnosed; however, at this point, the patient can still live and function independently. Patients are diagnosed with Alzheimer's dementia when there is impairment of two cognitive domains and these deficits significantly interfere with the ability of the patient to function independently at work or at home. Patients with memory loss as part of their MCI (also called amnestic MCI) are more likely to progress to AD, as are women, particularly those who are carriers of APOE ε4.[12-14]

As the disease progresses, patients become less and less independent and the caregiving impact increases. Eventually, many patients require around-the-clock in-home or institutional care. More than 11 million family members and other caregivers provided an estimated 15.3 billion hours of unpaid care to patients with AD or other dementias, putting these caregivers at risk for negative mental, physical, and emotional outcomes.[2] The average life expectancy for patients with AD depends on multiple factors including age, functional status at diagnosis, and comorbidities. Estimates range from four to eight years, but some patients live as many as 20 years after diagnosis.[2]

Treatment of AD remains largely supportive, including creation and implementation of individualized dementia care plans (e.g., treatment of dementia symptoms, medication and home safety assessments, advance care planning), caregiver education and support, care navigation, care coordination, and referral to community-based organizations for services (e.g., adult day care, caregiver training, etc.).[15] Non-pharmacologic treatments include physical activity, which some studies have suggested may prevent or mitigate AD[16,17] as well as behavioral strategies to ameliorate neuropsychiatric symptoms (e.g., agitation, delusions, disinhibition), and problem behaviors (e.g., resistance to care, hoarding, obsessive-compulsive behaviors).[18]

Pharmacological therapy of AD focuses on symptom management, since currently approved treatments have not been shown to substantially affect the disease trajectory. The most commonly prescribed drugs are the cholinesterase inhibitors, including donepezil, rivastigmine, and galantamine, and memantine, a drug that affects glutamine transmission. Cholinesterase inhibitors are indicated in mild, moderate, and severe AD, while memantine is approved for moderate-to-severe AD. These drugs, either alone or in combination, are often used to treat the cognitive and functional symptoms of the disease, despite limited evidence of efficacy and significant side effects.[19,20] Memantine was approved by the US Food and Drug Administration (FDA) in 2002; between 2002 and 2021, no new drugs targeted for treatment of AD were approved, other than a combination pill of extended-release memantine and donepezil.

Given the large and growing population of patients with AD and the economic and human burden of AD, there is a tremendous need for disease-modifying drugs (i.e., drugs that slow or stop progression of AD). To date, more than 20 drugs targeting purported molecular pathways of AD (e.g., beta-amyloid or tau proteins) have either failed in clinical trials or are still in development. Aducanumab ("aducanumab-avwa"; Aduhelm™, Biogen), a human monoclonal antibody, was the first disease-modifying drug to apply for approval from the FDA. Aducanumab promotes clearance of beta-amyloid plaques from the brain by selectively binding to aggregated oligomer forms of beta-amyloid, which is a different form of amyloid targeted by other anti-amyloid drugs. However, the role of the different forms of amyloid is not well understood, so the importance of targeting specific forms of amyloid for clearance is uncertain. Aducanumab is administered as an intravenous (IV) infusion every four weeks at a dosage of 10 mg/kg. The FDA granted approval to aducanumab for

all patients with AD on June 7, 2021 under the accelerated approval pathway, based on the surrogate endpoint of a reduction of beta-amyloid plaques in the brain, which it stated "is reasonably likely to result in clinical benefit."[21] The approval additionally requires a post-approval randomized controlled trial (RCT) to confirm clinical efficacy of the drug, to be completed by August 2029.[22]

2. Patient and Caregiver Perspectives

ICER engaged with patients with AD and caregivers, representatives from advocacy organizations, and clinical experts to understand the specific challenges associated with caring for patients with AD. Patients and patient groups emphasized the following issues, which are discussed in detail below: the underdiagnosis of AD, the lack of cohesive care after diagnosis, challenges of living with AD, impact on the caregiver, and outcomes other than cognition and function that are important to patients and their caregivers.

Although an estimated 10-30% of people over the age of 65 have AD, diagnosis is often missed or delayed. This may be in part due to lack of screening by primary care physicians, and the lack of an effective disease-modifying therapy. Furthermore, some patients with dementia may not be told of their diagnosis. Patients who are unaware or do not get diagnosed with AD at early stages may be missing opportunities for early intervention for symptoms, management of comorbidities that may contribute to worsening dementia, and planning for future care needs. Patient groups noted that the availability of a disease-modifying drug would likely lead to greater diagnosis of AD.

Patient groups described the lack of information that patients and caregivers receive about the disease after diagnosis. Many patients and their families do not receive adequate counseling about how to navigate the disease, including comprehensive care planning (e.g., functional assessment, review of current medications for high-risk medications, evaluation of home safety, caregiver needs, etc.), linkage to social services, management of comorbidities, information on participation in clinical trials, and end-of-life care. This may be partly due to limited treatments for the disease, limited time for physician counseling, and a lack of physician knowledge about a Medicare reimbursement code for care coordination.

Patients describe many challenges in living with AD. Early in the disease, some of the main challenges include dependence on others for driving, worry about being a burden on others for care, and the impact of the disease on mood, emotions, and social life and activities.[23] Later in the disease, the loss of memory and function impairs one's ability to complete activities of daily living, and caregiving needs increase. Ultimately, around-the-clock care becomes necessary, and patients may be moved to long-term care settings at this time. Because of the progressive nature of the disease and the older age of patients, the main goal of patients and caregivers is not to prolong life but instead to help patients remain independent, and they are eager for treatments that will help patients achieve this goal.

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 – often without training. Women are not only more likely to be caregivers but also to spend more time providing care than men. Surveys of caregivers show that they spend 40 to 60 hours per week directly caring for the patient; hours vary with

severity of disease and care setting.[4] Beginning early on in the disease, caregivers report impacts on their own lives including changes in their daily responsibilities, being less social, and decreasing or ceasing leisure activities.[23] Furthermore, there may be opportunity costs for caregivers, loss of work productivity, or need to leave the workforce early as they spend more time caring for the patient. As the disease progresses to moderate-to-severe dementia and the patient loses function, caregivers take on a greater physical and emotional load. For example, as patients moved from mild to severe AD, the financial, physical, psychosocial, social, and personal strain as measured by the Modified Caregiver Strain Index increased from an average score of 9.0 to 17.5 (out of a maximum of 26), indicating a substantial increase in caregiver impact.[4] Additionally, caregiver time burden may not substantially decrease when patients move to a long-term care setting.[24] Although caregivers may spend less time assisting with activities of daily living, that time may shift to activities such as supervising long-term care caregivers, advocating for the patient to ensure proper care, and managing the patient's finances and taking on increasing financial responsibility.

Caregivers who are heavily involved with the day-to-day care of the patient at home are more likely to continue this level of involvement once the patient has moved to long-term care.[23] Moreover, the impact of dementia on caregiver emotional well-being is significant, as caregivers may begin to grieve the loss of life that could have been as the disease progresses, and continue to grieve at later stages of the disease. As a result, caregivers often suffer physical and mental health consequences including increased chronic health conditions, depression and isolation, and increased use of the health care system.

The COVID-19 pandemic has especially challenged the AD community, as many patients with AD live in long-term care facilities, which were disproportionately affected with disease. In addition, many facilities were closed to visitors, increasing isolation and loneliness. Also, because patients with AD may have a hard time articulating their symptoms and rely on their caregivers to speak for them, without access to caregivers, some patients may not have had their medical and non-medical needs adequately addressed during this time. For AD patients living at home with caregivers, the pandemic resulted in increased difficulty accessing community-based care, which likely led to an increase in patient and caregiver stress.

An additional challenge of characterizing the impact of AD on patients and caregivers is the difficulty of collecting patient-important outcomes that accurately reflect all aspects of disease impact and caregiving. Many standardized measures capture cognition and function but may not simultaneously assess other important aspects of quality of life. For example, in addition to cognition and function, patients ranked emotional stability and well-being, preventing a "loss of self," becoming a burden on their families and caregivers, and personal safety as important outcomes to consider. Additionally, objective assessment of patients, particularly at later stages of the disease, may be difficult. While caregivers can provide important observations about patient symptoms and needs, they may introduce bias into current methods of assessing patient quality of

life. Additionally, caregiving patterns may differ in minority populations due to cultural factors and, thus, the caregiver who accompanies a patient to a study assessment, for example, may not be the patient's primary caregiver.

Clinicians also believe that the main goal of treatment for AD is not necessarily to extend life but to improve function and maintain independence. They also stated that effective disease-modifying drugs would be a welcome addition to the treatment arsenal. However, because there have been multiple disease-modifying drugs targeting amyloid that have previously failed during the clinical trial phase, some disease experts expressed doubt about whether amyloid is the main or only causal pathway for AD. Furthermore, since one of the main tenets of treating older adults is to minimize adverse effects, clinicians are cautious and feel they need clear evidence demonstrating a beneficial effect and minimal harm from a new therapy before recommending it broadly to patients.

3. Comparative Clinical Effectiveness

3.1. Methods Overview

Procedures for the systematic literature review assessing the evidence on aducanumab for early AD are detailed in the Supplement.

Scope of Review

We reviewed the clinical effectiveness of aducanumab plus supportive care versus supportive care alone for the treatment of early AD (i.e., MCI due to AD and mild AD dementia). We sought evidence on patient-important outcomes, including the ability to maintain independence and perform activities of daily living, delay entry into institutional care, preserve cognitive function, improve behavioral outcomes, and maintain health-related quality of life (HRQoL). We also sought evidence on caregiver impact and biomarker changes (e.g., level of beta-amyloid). The full scope of the review is detailed in the Supplement.

Evidence Base

Evidence informing our review of aducanumab was derived from two Phase III trials and one Phase Ib trial.[25] Because there were some differences in the trial objectives, dosing, design, and population enrolled in the Phase Ib trial, it was not a primary focus of our review. It is described in greater detail in the Supplement.

ENGAGE (also referred to as "Study 301") and EMERGE ("Study 302") were identically-designed and mostly contemporaneous Phase III trials that randomized 3,285 patients in a 1:1:1 ratio to low-dose aducanumab, high-dose aducanumab, or placebo (Table 3.1 on the following page).[25] Patients were eligible to participate if they were 50-85 years of age, met the criteria for either MCI due to AD or mild AD dementia, and had evidence of beta-amyloid pathology confirmed by PET. All patients received IV infusions of aducanumab or placebo every four weeks over a 78-week treatment period.

To mitigate the incidence of amyloid-related imaging abnormalities (ARIA), an adverse event associated with anti-amyloid drugs, dosages were titrated over a period of two to six months and dosing was determined by APOE ε4 carrier status.

In the low-dose group, APOE ε4 carriers received 3 mg/kg and non-carriers received 6 mg/kg. APOE ε4 carriers in the high-dose group also received 6 mg/kg, while non-carriers received 10 mg/kg. After data from the Phase Ib trial suggested it was safe to increase dosing in APOE ε4 carriers, investigators introduced a mid-study protocol amendment (Protocol Version 4 [PV4]) that had APOE ε4 carriers in the high-dose aducanumab arm titrate their dosage up to 10 mg/kg (Table 3.1).

At baseline, patients had a mean age of 70 and mean score on the Clinical Dementia Rating Scale – Sum of Boxes (CDR-SB) of 2.4 (the range for CDR-SB is 0-18, with higher scores indicating greater disease severity). Approximately two-thirds of the population were APOE ε4 carriers and 80% had a diagnosis of MCI due to AD (Table 3.1). Additional information about the trial population is available in the Supplement.

Table 3.1. Overview of Key Studies[25]

Trial	Population	Duration of Follow-Up	Dosing Schedule	Treatment Arms (n)	Key Baseline Characteristics
ENGAGE (Study 301)	Patients with MCI due to AD or mild AD dementia*	Planned 18-month double-blind, placebo-controlled treatment period followed by dose-blinded long-term extension Randomization stratified by APOE ε4 status	Dosing Protocol V. 1-3 Low-dose APOE ε4+ • 3 mg/kg Low-dose APOE ε4- • 6 mg/kg High-dose APOE ε4+ • 6 mg/kg High-dose APOE ε4- • 10 mg/kg Dosing Protocol V. 4-6 Low dose • Unchanged High dose • 10 mg/kg, regardless of APOE ε4 status	1. Low-dose ADU (n=547) 2. High-dose ADU (n=555) 3. Placebo (n=545) IV infusion every 4 weeks	**Age, mean (SD):** 70.1 (7.5) **APOE ε4 status, n (%)** APOE ε4+: 1145 (69.5) APOE ε4-: 499 (30.3) **Clinical stage, n (%)** MCI due to AD: 1325 (80.4) Mild AD: 322 (19.6) **CDR-SB score, mean (SD):** 2.41 (1.0)
EMERGE (Study 302)				1. Low-dose ADU (n=543) 2. High-dose ADU (n=547) 3. Placebo (n=548) IV infusion every 4 weeks	**Age, mean (SD):** 70.7 (7.4) **APOE ε4 status, n (%)** APOE ε4+: 1095 (66.8) APOE ε4-: 537 (32.8) **Clinical stage, n (%)** MCI due to AD: 1336 (81.6) Mild AD: 302 (18.4) **CDR-SB score, mean (SD):** 2.48 (1.0)

AD: Alzheimer's disease, ADU: aducanumab, APOE ε4+/-: apolipoprotein E4 carrier/non-carrier, CDR-SB: Clinical Dementia Rating-Sum of Boxes, IV: intravenous, MCI: mild cognitive impairment, mg/kg: milligram per kilogram, n: number, N: total number, SD: standard deviation

*Trial was monitored to enroll 80% of the population with participants who had a baseline clinical stage of MCI due to AD.

ENGAGE and EMERGE were terminated in March of 2019 following a prespecified interim analysis for futility that pooled data from both trials. At the time of data cutoff (December 26, 2018), the trials were trending in divergent directions.[25] Subsequent to the termination announcement, investigators sought to understand why the identical trials had yielded different results.

Accordingly, they examined an expanded dataset that included three additional months of data collected under double-blind, protocol-specified conditions between the data cutoff for futility and the public termination announcement. In this larger dataset, 60% of patients from the EMERGE trial and 66% of patients from the ENGAGE trial had the opportunity to complete the week 78 assessment.[25] The analysis suggested a favorable treatment effect from the EMERGE trial. In consultation with the FDA, the manufacturer conducted a series of analyses to explore the discrepant results. These analyses are described in the sections that follow.

3.2. Results

Clinical Benefits

Cognition and Function: CDR-SB

The primary efficacy endpoint in ENGAGE and EMERGE was the change from baseline in CDR-SB at week 78.[25] The CDR-SB is an instrument that assesses three domains of cognition (memory, orientation, judgment/problem-solving) and three domains of function (community affairs, home/hobbies, personal care) based on an interview with the patient or caregiver. The six domains are assigned a severity score ranging from 0 (no performance disability) to 3 (severe performance disability) and summed for a total possible score that ranges from 0 to 18. Higher scores suggest greater disease severity, and the minimal clinically important difference for CDR-SB is estimated to be 1 to 2 points.[26]

The CDR-SB results from ENGAGE and EMERGE appear to be discordant. In ENGAGE, there was no treatment benefit observed in either the high- or low-dose arms at week 78 (Table 3.2) A statistically significant difference in change from baseline in CDR-SB was observed in the high-dose arm of EMERGE (difference vs. placebo -0.39 [95% CI -0.69 to -0.09]), but not the low-dose arm. Although statistically significant, the change in CDR-SB score in the high-dose group was less than the 1 to 2 point change that has been suggested as a minimal clinically important difference.[25,26]

Table 3.2. CDR-SB Results from ENGAGE and EMERGE at Week 78, ITT Population[25,27]

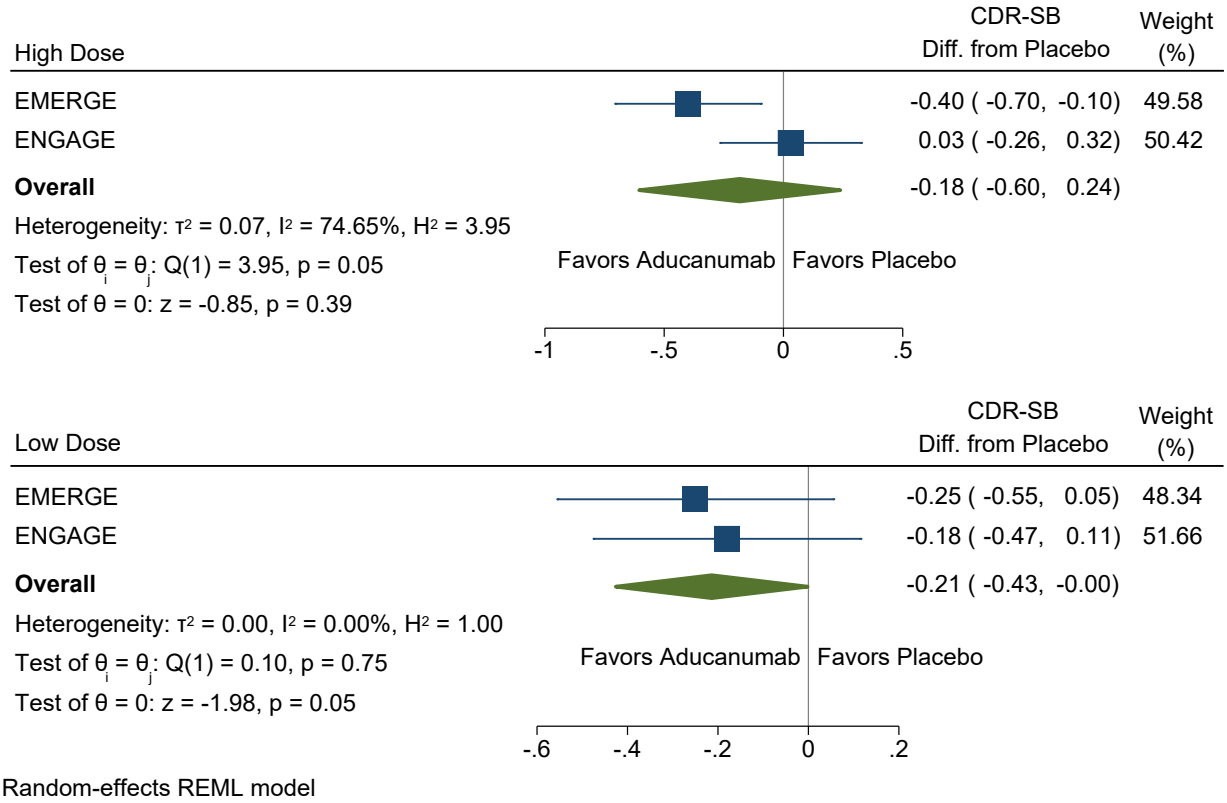
	ENGAGE			EMERGE		
	Placebo (n=545)	**ADU Low Dose (n=547)**	**ADU High Dose (n=555)**	**Placebo (n=548)**	**ADU Low Dose (n=543)**	**ADU High Dose (n=547)**
Baseline CDR-SB, Mean	2.40	2.43	2.40	2.47	2.46	2.51
Adjusted Mean Change From Baseline at Week 78 (95% CI)	1.56 (1.23, 1.77)	1.38 (1.16, 1.59)	1.59 (1.37, 1.81)	1.74 (1.51, 1.96)	1.47 (1.25, 1.70)	1.35 (1.12, 1.57)
Difference vs. Placebo (95% CI)	--	-0.18 (-0.47, 0.11)	0.03 (-0.26, 0.33)	--	-0.26 (-0.57, 0.04)	-0.39* (-0.69, -0.09)
% Difference vs. Placebo	--	-12%	2%	--	-15%	-22%
p-value (vs. Placebo)	--	0.2250	0.8330	--	0.0901	0.0120

ADU: aducanumab, CDR-SB: Clinical Dementia Rating-Sum of Boxes, CI: confidence interval, ITT: intention-to-treat
*p<0.05.

Supplementary analyses of the primary endpoint in the uncensored ITT population (i.e., including all data from before and after the decision to discontinue the aducanumab program was made public on March 21, 2019), and the opportunity-to-complete population (i.e., participants in the ITT population who had the opportunity to complete the week 78 visit by March 20, 2019) supported the results for each individual trial; the ENGAGE trial did not show statistically significant differences in CDR-SB scores across analysis populations, while the high-dose arm of the EMERGE trial remained statistically significant (see Supplement Table D13).

We pooled the primary endpoint results from ENGAGE and EMERGE in a pairwise meta-analysis (Figure 3.1). The pooled high-dose treatment effect was not statistically significant (difference in CDR-SB vs. placebo -0.18 [95% CI -0.50 to 0.24]); the low-dose results were similar but approached statistical significance (-0.21 [95% CI -0.43 to 0.00]). We also conducted a meta-analysis in the subset of patients who consented to PV4 prior to week 16; the pooled treatment effect from this analysis was more favorable than that of the ITT and statistically significant for both intervention arms (Supplement Figure D2).

Figure 3.1. Meta-Analysis of Difference in CDR-SB versus Placebo



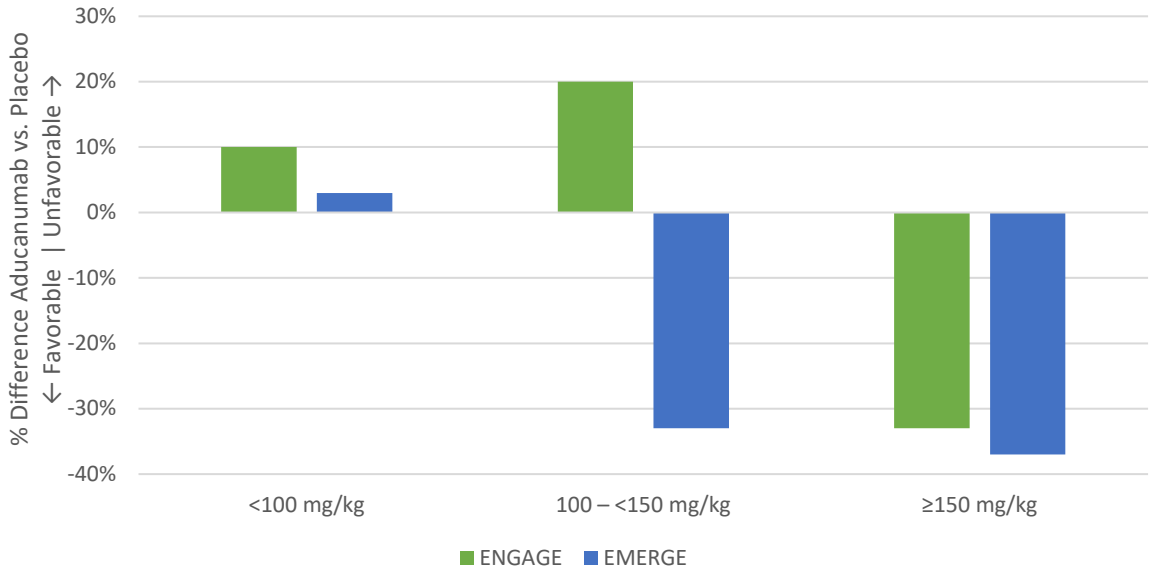
CDR-SB: Clinical Dementia Rating Scale-Sum of Boxes, CI: confidence Interval
The minimal clinically important difference for CDR-SB is estimated to be 1-2 points.

Post-Hoc Analyses of Post-Randomization Subgroups

Several post-hoc analyses were conducted by the manufacturer to explore possible explanations for the discordant results between ENGAGE and EMERGE. A key hypothesis for the negative results in ENGAGE was that participants did not receive sufficient dose exposure.[25] Specifically, two protocol amendments were implemented during the trials that altered the dosing strategy; Protocol Version 3 modified ARIA management to allow more patients to resume target dosing after resolution of the finding, and PV4 increased the target dose for APOE ε4 carriers in the high-dose arm from 6 to 10 mg/kg. These amendments were introduced earlier in the course of EMERGE, which started one month later than ENGAGE, and therefore allowed a higher percentage of patients in this trial to receive the full possible 14 doses of 10 mg/kg. Overall, 22.3% of patients in ENGAGE and 28.8% of patients in EMERGE received the maximum 14 doses of 10 mg/kg.[27]

Investigators stratified patients by both the total cumulative dose and the number of 10 mg/kg doses they received during the trial. Because these analyses were done based on post-randomization groupings, propensity score matching was used to match patients in the high-dose aducanumab arm with placebo subgroups (Figure 3.2 and Supplement Figures D3 and D4). The results of these analyses suggested that patients with the greatest cumulative exposure to aducanumab had similarly favorable changes in CDR-SB at 78 weeks in both ENGAGE and EMERGE, although results remained divergent at intermediate levels of exposure (i.e., 100-149 mg/kg and/or 6-12 doses of 10 mg/kg). The FDA's statistical reviewer raised concerns that the propensity score matching may have been inadequate.[25]

Figure 3.2. Post-Hoc Analysis of Adjusted Mean Change from Baseline in CDR-SB: % Difference from Propensity-Matched Placebo by Cumulative Dose Received[25]



kg: kilogram, mg: milligram

The FDA further explored the dosing hypothesis by assessing patients according to the timing of their consent to PV4, when the target dose for APOE ε4 carriers in the high-dose aducanumab arm increased from 6 to 10 mg/kg. Although the change in CDR-SB still did not reach statistical significance in the subset of ENGAGE participants who consented to PV4 prior to week 16, the point estimate moved in a favorable direction (from +0.03 in the ITT analysis to -0.48 in the post-PV4 subset).[28] As APOE ε4 carriers in the high-dose arm were the only participants to receive a dose increase with PV4, it would follow that their CDR-SB scores should improve after implementation of the protocol amendment, while other arms should have remained relatively stable. However, the change in CDR-SB scores at 78 weeks remained consistent in the high-dose-treated APOE ε4 carriers in EMERGE both pre- and post-PV4, while the placebo arm worsened post-PV4. In ENGAGE, there was a trend towards greater change in CDR-SB in the high-dose arm following PV4, although worsening in placebo response also occurred post-PV4. Thus, it is difficult to assess whether the more favorable results following implementation of PV4 was due to greater exposure to aducanumab, or to placebo worsening, or both.

Non-APOE ε4 carriers in the high-dose arm, who were not affected by the PV4 amendment, might have been expected to have better CDR-SB scores based on the dosing hypothesis. These individuals received 10 mg/kg for the duration of both Phase III trials and experienced fewer dose reductions or interruptions from ARIA relative to APOE ε4 carriers. However, there was only a modest, non-statistically-significant treatment effect among non-APOE ε4 carriers in both trials (CDR-SB change vs. placebo of -0.07 in both ENGAGE and EMERGE).[25] The results could indicate heterogeneity of treatment effect by carrier status, although it is difficult to disentangle this possibility from the simultaneous placebo worsening that may have driven the more favorable results in the APOE ε4 carrier group.

A final challenge to the dosing hypothesis is that patients in the low-dose group of ENGAGE received no doses of 10 mg/kg and had lower cumulative dosing overall, yet had a more favorable point estimate than the high-dose group (Table 3.2).

Additional Hypotheses to Explain Discordant Results: Rapid Progressors and ARIA

Together with the FDA, the manufacturer explored additional hypotheses for the discordant results in ENGAGE and EMERGE. The high-dose arm included a higher number (n=9) of individuals who were identified post-hoc as "rapid progressors" (i.e., participants whose CDR-SB score worsened ≥8 points over 78 weeks) than the other arms of both trials (n=4-5).[25] When these individuals were removed from the dataset, the difference in CDR-SB score versus placebo in the high-dose arm of ENGAGE changed from 0.03 to a slightly improved score of -0.09 (95% CI not reported). The FDA's statistical reviewer noted that both trials had blinded sample size increases from 450 to 535 patients in each group, which should have helped offset the impact of the few rapidly progressing individuals. Furthermore, additional analyses using robust regression and trimmed means to

address outliers also did not suggest a treatment benefit for the high-dose arm of aducanumab in ENGAGE.

Another hypothesis for the different trial outcomes was the possibility that discordant rates of ARIA in ENGAGE and EMERGE could have contributed to different levels of functional unblinding. Given that ARIA disproportionately affected aducanumab-treated patients (41% of the high-dose arm experienced ARIA vs. 10% of the placebo arm), and its management required additional follow-up MRIs and dose suspension, its occurrence could have alerted patients and their caregivers that they were receiving active therapy. The CDR-SB, which is measured through interviews with patients and caregivers, could therefore be susceptible to biased estimates if respondents knew they were on therapy.

The incidence and severity of ARIA was similar in both trials, so this was unlikely the cause of the different trial outcomes, although it remains unclear whether functional unblinding from participants may have biased the results. A post-hoc analysis of the CDR-SB that excluded all assessments after the occurrence of ARIA yielded results that were consistent with the primary analysis (Supplement Table D4). Similar analyses of the Mini-Mental State Exam (MMSE), which is a performance-based endpoint that may be less susceptible to bias from unblinding than the CDR-SB, also remained consistent. However, the subgroups who experienced the least amount of ARIA (i.e., APOE ε4 non-carriers) and therefore less potential unblinding, did not appear to derive benefit from aducanumab. Reasons for this discordance are uncertain.

Other Measures of Cognitive Performance, Function, and Behavior

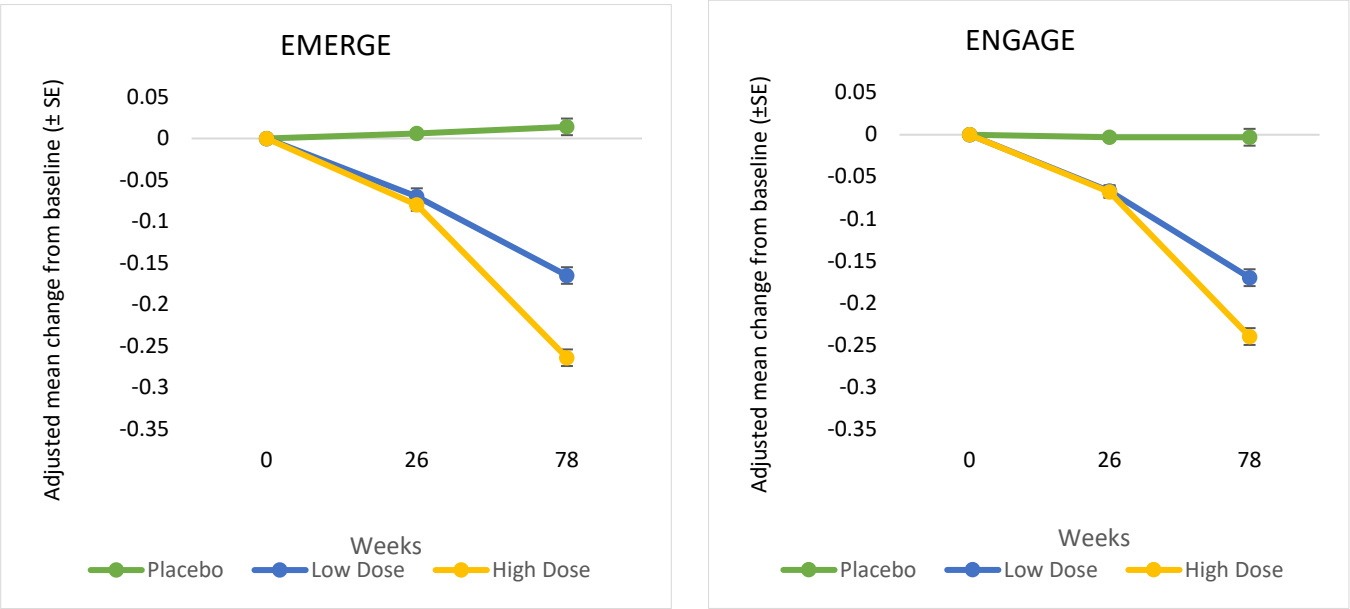
Other measures of cognition, function, and behavior such as the MMSE, Alzheimer's Disease Assessment Scale – Cognitive Subscale-13-Item Version (ADAS-Cog 13), Alzheimer's Disease Cooperative Study-Activities of Daily Living-MCI (ADCS-ADL-MCI), and Neuropsychiatric Inventory 10 (NPI-10) were directionally consistent with the respective primary endpoint results of ENGAGE and EMERGE. The changes in secondary endpoints were nominally statistically significant in EMERGE; none of these endpoints reached statistical significance in ENGAGE. These are described in greater detail in the Supplement.

Changes in AD-Related Biomarkers

Change from baseline in brain amyloid, as measured by PET composite standard uptake value ratio (SUVR), appeared to be time- and dose-dependent (Figure 3.3).[25] At week 26, when dosing was similar across treatment arms due to titration, the adjusted mean change from baseline relative to placebo was similar in the low-dose and high-dose groups of both trials. Further decreases in amyloid plaque were apparent at week 78, when the adjusted mean change from placebo was -0.179 and -0.278 in the low- and high-dose arms of EMERGE, respectively, and -0.167 and -0.232 in

the low- and high-dose arms of ENGAGE, respectively. Additional markers of downstream AD pathophysiology are reported in the Supplement.

Figure 3.3. Change from Baseline in AB PET Composite SUVR in EMERGE and ENGAGE[25]



PET: positron emission tomography, SE: standard error, SUVR: standardized uptake value ratio

Harms

Pooled safety data from ENGAGE and EMERGE report that 90.7% of participants receiving aducanumab experienced an adverse event as compared to 86.9% in the placebo arm.[25] The more common adverse events included ARIA, headache, fall, and diarrhea. Adverse events leading to drug discontinuation were reported in 9.1% of aducanumab-treated participants versus 4.1% in the placebo arm.

Across the aducanumab clinical development program, 31 deaths were reported, of which 16 occurred during the Phase III trials (Table 3.3); all but one of these deaths have been deemed by investigators to be unrelated to study treatment.[25] One patient in the aducanumab arm of the Phase Ib trial died of an intracranial hemorrhage believed to be related to study treatment.

Table 3.3. Overview of Pooled Aducanumab Safety Data for ENGAGE and EMERGE at 78 Weeks[25,27]

	Patients, n (%)				
	Placebo (N=1087)	ADU 3 mg/kg (N=760)	ADU 6 mg/kg (N=405)	ADU 10 mg/kg (N=1033)	Total for ADU Arms (N=2198)
AE	945 (86.9)	700 (92.1)	347 (85.7)	946 (91.6)	1993 (90.7)
Study Drug-Related AE	273 (25.1)	373 (49.1)	148 (36.5)	530 (51.3)	1051 (47.8)
Serious AE	151 (13.9)	105 (13.8)	54 (13.3)	141 (13.6)	300 (13.6)
Serious Study Drug-Related AE	8 (0.7)	9 (1.2)	7 (1.7)	21 (2.0)	37 (1.7)
Deaths	5 (0.5)	3 (0.4)	0 (0)	8 (0.8)	11 (0.5)
Study Drug Discont. Due to AE	45 (4.1)	65 (8.6)	45 (11.1)	91 (8.8)	201 (9.1)
ARIA-E or ARIA-H	111 (10.3)	274 (36.2)	104 (26.5)	425 (41.3)	803 (36.9)
ARIA-E	29 (2.7)	223 (29.3)	83 (20.5)	362 (35.0)	668 (30.4)
ARIA-H	94 (8.7)	193 (25.5)	63 (16.1)	291 (28.3)	547 (25.1)
Headache	165 (15.2)	161 (21.2)	58 (14.3)	212 (20.5)	431 (19.6)
Fall	128 (11.8)	105 (13.8)	50 (12.3)	155 (15.0)	310 (14.1)
Diarrhea	74 (6.8)	62 (8.2)	27 (6.7)	92 (8.9)	181 (8.2)

ADU: aducanumab, AE: adverse event, ARIA-E/H: amyloid-related imaging abnormalities-edema/effusion or hemorrhage/superficial siderosis, discont.: discontinuation, mg/kg: milligram per kilogram, N: total number

ARIA

A safety event of special interest in the Phase III trials was ARIA due to edema/effusion (ARIA-E) or brain microhemorrhage or localized superficial siderosis (ARIA-H). Monitoring and management practices such as titration over 24 weeks, routine and follow-up MRI scans, and temporary dose suspension were used to minimize incidence of ARIA. Participants had five scheduled brain MRIs during the first year of the treatment period and two MRIs scheduled during the last six months. Protocol Versions 4-6 specified that patients with asymptomatic mild ARIA could continue on the drug; if participants experienced moderate or severe asymptomatic ARIA and/or any symptomatic ARIA, dosing was suspended until the findings resolved. Participants could resume treatment at the same dose following resolution unless they experienced serious symptomatic ARIA; for these severe cases, treatment was permanently discontinued.[25]

In the high-dose arm of the two Phase III trials, 41.3% of participants experienced ARIA compared to 10.3% in the placebo arm (Table 3.3) and these events occurred more commonly in APOE ε4 carriers (Table 3.4).[25] Both ARIA-E and ARIA-H were observed at higher rates in all aducanumab arms (3, 6, or 10 mg/kg) relative to the placebo arm.

Across the two trials, ARIA-E and ARIA-H occurred in 35.0% and 28.3% of high-dose-treated patients, respectively, compared with 2.7% and 8.7% of patients in the placebo arms, respectively. The majority of reported cases of ARIA-E were asymptomatic: 74.0% of cases in the high-dose aducanumab arm and 89.7% of cases in the placebo arm.[24] ARIA symptoms were generally mild or moderate and in the high-dose aducanumab arm included headache (46.6%), confusion (14.6%),

and dizziness (10.7%). Within the cases of ARIA-H, 19.1% experienced microhemorrhage, 0.3% experienced macrohemorrhage, and 14.7% experienced superficial siderosis.

Table 3.4. Pooled ARIA-E Incidence by APOE ε4 Status in ENGAGE and EMERGE[27]

		Patients, n/N (%)	
		Placebo	ADU 10 mg/kg
ARIA-E	Overall	29/1076 (2.7)	362/1029 (35.0)
	APOE ε4 Carrier	16/742 (2.2)	290/674 (43.0)
	APOE ε4 Non-Carrier	13/334 (3.9)	72/355 (20.3)

APOE ε4: apolipoprotein E4, ARIA-E: amyloid-related imaging abnormalities-edema/effusion, mg/kg: milligram per kilogram, n: number, N: total number

During the trials, ARIA-E occurred early in treatment and incidence increased over time. Estimates of time to first ARIA-E event in the 10 mg/kg arm across both trials show most first events of ARIA-E occurring within the first eight doses of aducanumab (32 weeks after starting treatment). At week 32 in the high-dose arm, the estimated proportion with ARIA-E was approximately 0.258 (95% CI: 0.232, 0.286) and this increased to 0.387 (95% CI: 0.351, 0.424) by week 80.[25] Additional data on time to first ARIA-E event can be found in the Supplement.

ARIA symptoms were generally mild or moderate and in the high-dose aducanumab arm included headache (46.6%), confusion (14.6%), and dizziness (10.7%). Serious ARIA-E was reported in 13 participants in the high-dose arm and one participant in the placebo arm. Most ARIA-E events (98%) resolved during the treatment period, with 69% resolving within 12 weeks. ARIA led to discontinuation of study therapy in 6.2% of participants receiving the high dose of aducanumab and 0.6% of participants in the placebo arm.

Subgroup Analyses and Heterogeneity

Pre-Specified Subgroup Analyses

The Phase III trials of aducanumab evaluated 16 total subgroups defined by baseline demographic and disease characteristics. At present, there is only limited subgroup information available from the ENGAGE trial. Consistent trends were not observed across results stratified by APOE ε4 carrier status, nor race (Table 3.5). A relatively larger treatment effect was observed in APOE ε4 carriers in the EMERGE trial, which may have been a reflection of the more rapid worsening in the placebo group in this arm. We did not identify any efficacy or safety data specific to patients with amnestic (vs. non-amnestic) MCI.

Table 3.5. Pre-Specified Subgroup Analyses of CDR-SB in EMERGE and ENGAGE[25]

	ENGAGE		EMERGE	
	Placebo Decline	High-Dose ADU Adjusted Mean Change vs. Placebo (SE)	Placebo Decline	High-Dose ADU Adjusted Mean Change vs. Placebo (SE)
APOE ε4 Carrier	NR	+0.07 (0.18)	1.93	-0.54 (0.19)
APOE ε4 Non-Carrier	NR	-0.07 (0.27)	1.30	-0.07 (0.27)
Asian	NR	0.07 (0.51)	NR	-1.06 (0.68)
White	NR	-0.16 (0.17)	NR	-0.39 (0.17)
Other Race	NR	1.02 (0.40)	NR	-0.30 (0.39)

ADU: aducanumab, APOE ε4: apolipoprotein E4, CDR-SB: Clinical Dementia Rating-Sum of Boxes, NR: not reported, SE: standard error

Uncertainty and Controversies

EMERGE is the first late-stage clinical trial of drugs targeting removal of amyloid—out of more than 25 RCTs examining such therapies—to show clinical efficacy. This may be due to lessons learned from earlier trials, such as enrolling patients at earlier stages of disease (MCI and mild AD), before substantial neuronal damage and when amyloid clearance may have more of an impact, or due to better patient selection by confirming AD through documentation of beta-amyloid presence in the brain prior to enrollment. Although EMERGE met its primary endpoint, its parallel sister trial ENGAGE did not, despite no difference in baseline characteristics between the two trials.

While beta-amyloid has been strongly implicated in the pathogenesis of AD, the relationship between reduction in brain amyloid burden and slowing of cognitive decline has not been fully established, nor is the role of the different forms of amyloid fully understood, so the impact of targeting certain forms of amyloid is uncertain. Although aducanumab-treated participants in both trials had substantial clearance of beta-amyloid compared with placebo, and there was a positive correlation between level of beta-amyloid and CDR-SB in a sub-study of 329 patients in EMERGE, the correlation was relatively weak, and was not shown in a similar sub-study done with ENGAGE patients. Prior late-stage clinical trials of drugs targeting the removal of amyloid have not shown clinical efficacy,[29] calling into question whether removal of amyloid alone is sufficient to delay cognitive decline or reverse decline that has already occurred, although amyloid clearance appeared to be less substantial in those trials than was seen with aducanumab.[29]

A number of methodologic issues raise concerns about interpretation of the evidence. These issues, summarized here and discussed in detail in the Supplement, include:

- Analysis of a trial stopped for futility
- Use of the Phase Ib trial to provide a "second" positive trial
- Analyses excluding "rapid progressors"
- Effect of functional unblinding due to ARIA

- Post-hoc analysis of trial results.

As discussed in the Supplement, we think it is unlikely that there were important threats to validity from analyzing the trials after stopping for futility or from functional unblinding due to ARIA. In contrast, we think the exclusion of rapid progressors and the performance of multiple post-hoc analyses to explain the discordant studies represent potentially very serious threats to validity. We also discuss how one might consider evidence from the Phase Ib trial, which provided evidence of efficacy but was small and had differential drop-out rates in the treatment and placebo groups, which may limit its utility as a supportive study.

While the primary outcome of CDR-SB is a validated scale and used as an outcome in clinical trials, a minimal clinically important difference has not been established. Although the FDA accepted any statistically significant change in CDR-SB as a clinically meaningful outcome, there is a difference of opinion on this point and some experts have suggested that the minimal clinically important difference is on the order of 1 or 2 points.[26] In this context, the absolute difference in CDR-SB of 0.39 points seen in EMERGE, while statistically significant, may or may not be representative of a change in status that is clinically meaningful to patients, caregivers, or clinicians.

Cognitive decline in MCI and mild AD generally occurs over years, and thus the 78-week follow-up duration may not be sufficient to conclude whether a drug is effective for early AD or whether the safety profile might change with longer follow-up. In addition, aducanumab received broad approval for all stages of the disease, even though the trial populations were limited to patients with early AD; it is unknown whether aducanumab is effective or safe for patients with moderate or severe AD. Longer-term follow-up data from patients enrolled in the ENGAGE and EMERGE trials are currently being collected in an open-label study called EMBARK, scheduled to be completed in 2023.

Although the majority of ARIA cases were asymptomatic, there were reports of serious symptoms. While ARIA was detected early by frequent MRI monitoring in the clinical trials, this level of careful monitoring may prove to be more challenging to implement in routine clinical care, particularly when involving patients who are older than the trial participants. Moreover, the FDA prescribing information for aducanumab requires just two MRIs after initiation of therapy, prior to the first and sixth 10 mg/kg treatment (compared to seven in ENGAGE and EMERGE). Thus, ARIA may pose greater risks to patients who may be older, have more comorbidities, and are less carefully monitored outside of clinical trials.

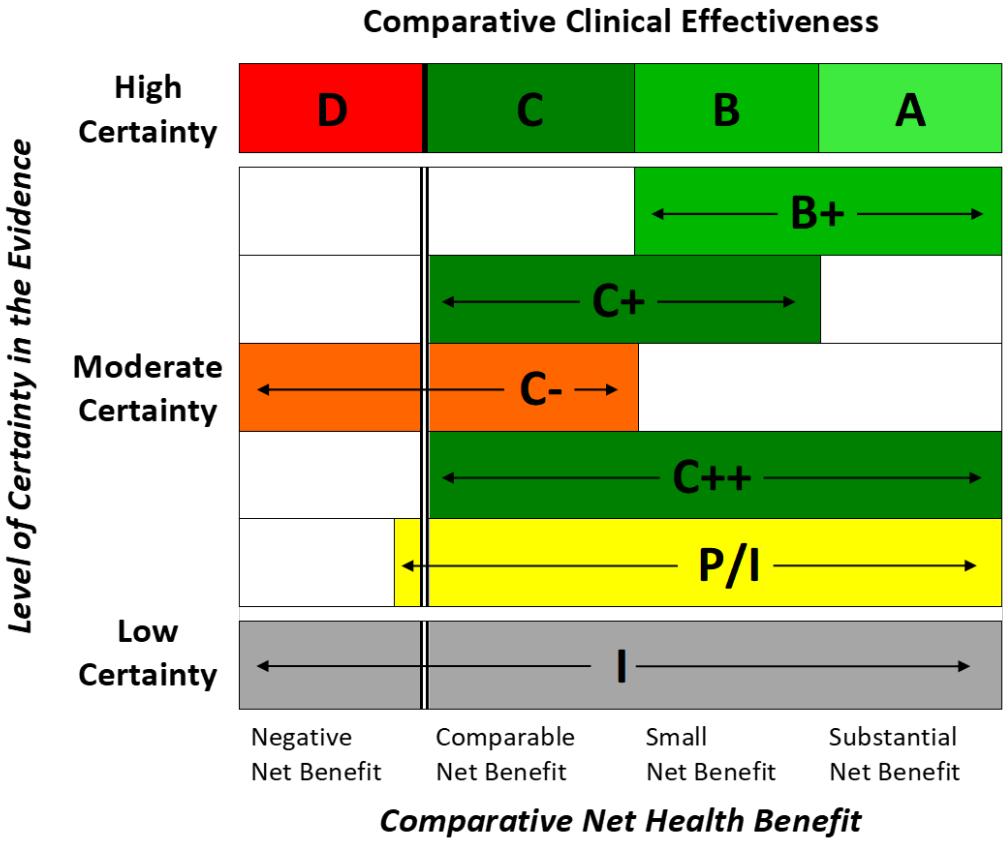
Although ENGAGE and EMERGE were multinational trials, there was a lack of racial and ethnic diversity in the trial population, with the majority of participants being White; out of 3,268 total individuals who participated in ENGAGE and EMERGE, just 19 (0.6%) were Black or African American and 104 (3.2%) were Hispanic or Latino. Additionally, the average age of the clinical trial population was 70 years old, and the upper age limit of inclusion in the trial was 85 years of age. Given that the

prevalence of AD is higher in Black and Hispanic Americans and more than one-third of patients with AD in the US are over the age of 85, a lack of representation of these groups in the trial population could limit the generalizability of the results to the broader US population.

3.3. Summary and Comment

An explanation of the ICER Evidence Rating Matrix (Figure 3.4) is provided here.

Figure 3.4. ICER Evidence Rating Matrix



A = "Superior" - *High certainty of a substantial (moderate-large) net health benefit*
B = "Incremental" - *High certainty of a small net health benefit*
C = "Comparable"- *High certainty of a comparable net health benefit*
D= "Negative"- *High certainty of an inferior net health benefit*
B+= "Incremental or Better" – *Moderate certainty of a small or substantial net health benefit, with high certainty of at least a small net health benefit*
C+ = "Comparable or Incremental" - *Moderate certainty of a comparable or small net health benefit, with high certainty of at least a comparable net health benefit*
C- = "Comparable or Inferior" *– Moderate certainty that the net health benefit is either comparable or inferior with high certainty of at best a comparable net health benefit*
C++ = "Comparable or Better" - *Moderate certainty of a comparable, small, or substantial net health benefit, with high certainty of at least a comparable net health benefit*
P/I = "Promising but Inconclusive" *- Moderate certainty of a small or substantial net health benefit, small (but nonzero) likelihood of a negative net health benefit*
I = "Insufficient" – *Any situation in which the level of certainty in the evidence is low*

ENGAGE and EMERGE were identically-designed, mostly contemporaneous trials with discordant results. While EMERGE met its primary endpoint, providing a glimmer of hope for patients and caregivers who have long awaited a breakthrough for this devastating disease, ENGAGE did not. In fact, the high-dose arm's change in CDR-SB score in ENGAGE was numerically worse than placebo at 78 weeks.

The manufacturer examined several hypotheses to try to explain why the trials produced such different outcomes, yet these analyses can be considered exploratory at best. The post-hoc nature of these analyses resulted in a loss of randomization, which limits the conclusions that can be drawn from them. Moreover, other patterns in the data challenge the face validity of the hypotheses that were explored. For example, the theory positing that sustained exposure to the 10 mg/kg dose is required for benefit cannot be disentangled from potential subgroup effects or placebo decline. Furthermore, the degree of improvement seen in EMERGE is of uncertain clinical significance, and the relationship between clearance of beta-amyloid in the brain and clinical improvement has yet to be conclusively demonstrated. We are unable to dismiss the ENGAGE trial's negative findings, and thus cannot rule out the possibility that EMERGE may have produced chance findings.

In addition, we remain concerned about the safety profile of aducanumab. ARIA was common in the treatment groups, with over one-third of patients experiencing this adverse event, and serious symptoms leading to discontinuation of the drug occurred in 6% of patients. Additionally, the level of careful monitoring (e.g., with frequent MRIs) performed in clinical trials is not required by the FDA labeling. Given that between 15-20% of patients developed ARIA-E within the first six months of treatment, less frequent monitoring in routine clinical care could lead to more severe consequences of ARIA than reported in the trials. Even in the carefully controlled environment of the clinical trials, serious cases of ARIA still occurred. Furthermore, the long-term impact of ARIA episodes (e.g., the possibility of more severe cognitive decline later in the disease) is unknown.

The need for disease-modifying treatment for patients with AD is great, however, it is unclear that treatment with aducanumab provides net health benefits to patients. Given the certainty that harms can occur in patients treated with aducanumab and uncertainty about benefits, we rate the evidence to be *insufficient* to determine the net health benefit of aducanumab ("I") in patients with MCI and mild AD. Although clinical trials for aducanumab did not include patients with moderate or severe AD, prior clinical trials of anti-amyloid drugs have suggested a lack of benefit in this population, and thus the potential that aducanumab would benefit patients with severe forms of AD is even less likely.

CTAF Votes

During ICER public meetings, CTAF deliberates and votes on key questions related to the systematic review of the clinical evidence, an economic analysis of the applications of treatments under examination, and the supplementary information presented. Panel members are not pre-selected based on the topic addressed and are intentionally chosen to represent a range of expertise and diverse perspectives.

Acknowledging that judgment of evidence is strengthened by real-world clinical and patient perspectives, subject-matter experts are recruited for each meeting topic and provide input to CTAF before the meeting to help clarify their understanding of the different interventions analyzed in the evidence review. The same clinical experts serve as a resource to CTAF during their deliberation and help to shape recommendations on ways the evidence can apply to policy and practice.

Voting results for comparative clinical effectiveness may be found below; results for other benefits and contextual considerations and long-term value for money may be found in Sections 5 and 6, respectively.

Table 3.7. CTAF Votes on Comparative Clinical Effectiveness

Question	Yes	No
Is the available evidence adequate to demonstrate that the net health benefit of aducanumab plus supportive care is superior to that provided by supportive care alone?	0	15

CTAF voted unanimously that the evidence is not adequate to demonstrate that aducanumab is superior to supportive care. CTAF cited the discordant results from ENGAGE and EMERGE as well as the fact that the degree of improvement seen in EMERGE is of uncertain clinical significance. Further, it was noted that the relationship between beta-amyloid clearance and clinical benefit has yet to be demonstrated.

4. Long-Term Cost Effectiveness

4.1. Methods Overview

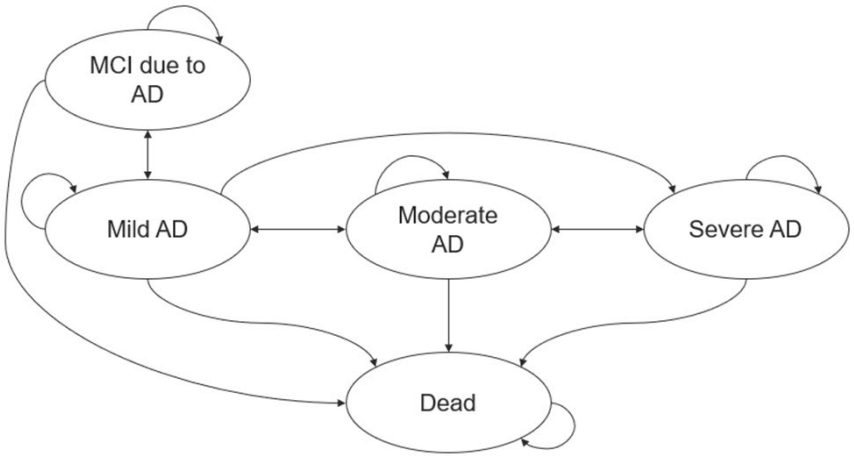
The primary aim of this analysis was to estimate the cost effectiveness of aducanumab in addition to supportive care as compared to supportive care alone. We developed a *de novo* Markov model for this evaluation, informed by key clinical trials and prior relevant economic models. Our analysis reports results from two perspectives: a health care system perspective (i.e., focusing on the direct medical care costs and health outcomes of the patient) and a modified societal perspective (i.e., including patient productivity impacts, caregiver time spent caregiving, caregiver quality of life, and caregiver direct medical costs). Even though the impact of treatment with aducanumab on modified societal costs was not substantial (as described in the ICER Reference Case), these are presented as co-base-case analyses given the enormity of these costs in AD.

The model consisted of five health states that tracked the severity of disease, including MCI due to AD, mild AD, moderate AD, severe AD, and death (Figure 4.1 on the following page). Although the model is flexible to include many bi-directional arrows, the evidence suggests that the vast majority do not improve over time. All health states could transition to the dead health state due to all-cause and disease-specific mortality. Model cycle length was one year as has been used in prior published economic models and in clinical evidence.[30-33] Specific to each health state, the model also tracked the setting of care (e.g., community or long-term care). Patients were able to transition from community to long-term care; however, once in long-term care, they remained there until death. Individuals remained in the model until they died.

Model outcomes included quality-adjusted life years (QALYs) gained, equal-value of life years gained (evLYG), total life years (LYs) gained, total years living outside of long-term care, and total costs over a lifetime time horizon. Outcomes are reported as discounted values, using a discount rate of 3% per year.

Changes to the economic evaluation between the draft Evidence Report and this version included updating the price of aducanumab and updating the number of MRIs patients receive while taking aducanumab. During the time between our draft Evidence Report and this version, the manufacturer announced an average annual price of $56,000 per year. In our draft Evidence Report, we used a placeholder price of $50,000 based on market analyst estimates. In this report, we have updated the annual price to $56,000 (plus a 6% mark-up for infusion). This increase in price resulted in less favorable incremental cost-effectiveness ratios. Also, during the time between our draft Evidence Report and this report, the FDA label for aducanumab became available. We reduced the number of MRIs that were included in our model to align with the FDA label. This resulted in small increases to the health-benefit price benchmarks.

Figure 4.1. Model Structure



AD: Alzheimer's disease, MCI: mild cognitive impairment

Population

In alignment with the clinical evidence and updated FDA label, the starting population for the economic evaluation included adults with early AD, defined as MCI due to AD or mild AD. Consistent with population estimates, slightly more than half (55%) of the cohort started in the MCI due to AD health state, with the remaining cohort (45%) starting in the mild AD health state. Patients could progress to more severe AD health states over the model time horizon. The majority of the cohort (92%) started the model in a community setting of care. Additional patient characteristics are described in more detail in Supplement Table E2.

Interventions

The list of interventions was developed with input from patient organizations, clinicians, and manufacturers on which treatments to include. The only intervention identified was aducanumab. Aducanumab was evaluated as an addition to supportive care.

Comparator

The comparator for aducanumab was supportive care, which can include non-pharmacologic and pharmacologic, but not disease-modifying, interventions.

4.2. Key Model Assumptions and Inputs

Our model includes several assumptions and key choices, many of which are stated in Table 4.1. Additional assumptions can be reviewed in Supplement Table E3.

Table 4.1. Key Model Choices and Assumptions

Model Choice or Assumption	Rationale
Patients stop receiving aducanumab once they enter the severe AD health state.	During conversations with experts, we heard that active treatments, particularly IV-administered treatments, often stop once an individual has reached severe AD. We relaxed this assumption in a separate scenario analysis.
Aducanumab reduces disease progressions from the MCI and mild AD health states.	Currently available efficacy evidence for aducanumab is within the MCI due to AD and mild AD health states. Evidence is insufficient and uncertain. The uncertainty in these estimates was extensively tested through sensitivity and scenario analyses.
Aducanumab does not reduce or increase the rate of disease progression from the moderate AD health state.	Stakeholders suggested there is likely no effect with aducanumab at reducing disease progression once a patient has reached moderate AD. For transitions out of moderate AD, we assumed a hazard ratio of 1.0. Thus, we assumed there was no benefit of reducing disease progression (i.e., hazard ratio not less than 1), but we also assumed no slope worsening or catch-up period in moderate AD (i.e., hazard ratio greater than 1) given that patients would remain on treatment. In this way, a hazard ratio equivalent to 1 suggests that any benefit assigned at slowing earlier transitions would not be diminished by way of faster subsequent transition (i.e., moderate to severe).
Aducanumab is 50% less effective on transitions out of mild AD than it is on transitions out of MCI due to AD.	There is very limited evidence on the effectiveness of aducanumab on the mild AD to moderate AD transition given the clinical characteristics and early disease stages of the trial participants. We believe the effectiveness in the mild AD health state must be somewhere between the effectiveness for the MCI health state and the absence of a reduction in disease progression assumed in the moderate AD health state. We thus assumed the effectiveness in the mild AD health state is the midpoint of those numbers – half of the effectiveness in the MCI health state. This assumption was extensively tested through sensitivity analyses.
Aducanumab's effect on health state transitions will equate to its relative effect on changes in CDR-SB where evidence on health state transitions is not available.	The preference was for evidence on health state transitions. When that evidence was not available, the CDR-SB, as one of the most commonly used metrics to assess the severity of AD, was a proxy.

AD: Alzheimer's disease, CDR-SB: Clinical Dementia Rating-Sum of Boxes, IV: intravenous, MCI: mild cognitive impairment

Model inputs were identified from best-available evidence and stakeholder engagement. The primary clinical inputs included the transition probabilities among alive health states, mortality, progressions to long-term care, aducanumab efficacy, the occurrence of adverse events, and discontinuation. Utility estimates were retrieved for both the patient and caregiver. The primary cost inputs included aducanumab acquisition costs, administration costs, monitoring costs, adverse event costs, long-term care costs, and other patient medical and pharmacy costs. Costs to inform the societal perspective included patient productivity, caregiver productivity, and caregiver health care costs. Select model inputs can be reviewed in Table 4.2 on the following page, but a detailed description of each input that informed the model can be found in Section E of the Supplement.

Table 4.2. Key Model Inputs

Parameter	Value	Source	Notes
Aducanumab HR for Patients Progressing from MCI Due to AD	0.86	Biogen data on file[34] and FDA AdComm Briefing Document[35]	Applied to MCI to mild AD transition; calculated from weighted avg. based on trials' sample; used 1.02 for ENGAGE trial based on CDR-SB and 0.69 based on health state transition HR provided by Biogen
Aducanumab HR on Patients Progressing from Mild AD	0.93 (50% as effective as HR for patients progressing from MCI)	Assumption	Applied to mild to moderate and mild to severe transition
Aducanumab HR on Patients Progressing from Moderate AD	1.0	Assumption	Stakeholders suggested there is likely no effect with aducanumab at reducing disease progression once patient reaches moderate AD
Probability of Symptomatic ARIA/Discontinuation Due to AEs	10%	FDA AdComm Briefing Document[35]	Occurred within first 18 months of starting aducanumab; discontinuation not related to AEs occurred as individuals transitioned to severe AD over the time horizon
Duration of ARIA	12 weeks	FDA AdComm Briefing Document[35]	Duration influenced disutility and monitoring costs
Patient Disutility (Community; LTC) **MCI Due to AD** **Mild AD** **Moderate AD** **Severe AD**	 -0.17; -0.17 -0.22; -0.19 -0.36; -0.42 -0.53; -0.59	Calculated from utility estimates and patient demographics in Neumann et al., 1999[32,36]	Duration of occupancy in health state and setting of care
Caregiver Disutility (Community; LTC) **MCI Due to AD** **Mild AD** **Moderate AD** **Severe AD**	 -0.03; -0.03 -0.05; -0.05 -0.08; -0.08 -0.10; -0.10	Calculated from utility estimates and patient demographics in Neumann et al., 1999[32,36]; adjusted for AD severity using relationship from Mesterton et al., 2010[37]	Duration of occupancy in health state and setting of care; applied in analysis from societal perspective
Aducanumab Annual Cost	$59,360	Manufacturer[38]	Manufacturer provided price of $56,000* plus 6% due to infusion; first-year cost was $41,344 due to dose titration in first year
Caregiver Time Spent Caregiving for Community-Dwelling Patients **MCI Due to AD** **Mild AD** **Moderate AD** **Severe AD**	 69 hours/month 113 hours/month 169 hours/month 298 hours/month	Robinson et al., 2020[39] and Haro et al., 2014[40]	Estimates are for amyloid-positive patients where available; caregiver time spent caregiving for LTC-dwelling patients was 44% of time spent for community-dwelling patients[41]

AD: Alzheimer's disease, AdComm: Advisory Committee, AE: adverse event, ARIA: amyloid-related imaging abnormalities, HR: hazard ratio, LTC: long-term care, MCI: mild cognitive impairment

*The model used $56,000 per year (plus 6%) after year one based on estimates reported by the manufacturer, but the price would actually be $56,056 (plus 6%) based on the WAC and accounting for vial wastage.

4.3. Results

Base-Case Results

Supplement Tables E18 and E19 present the percent on treatment over the time horizon and average time spent in each health state, respectively. The total discounted costs, QALYs, evLYs, life years, and years in the community over the lifetime time horizon are detailed in Table 4.3. Treating patients with aducanumab resulted in approximately $204,000 greater costs over the lifetime time horizon, but only around 0.154 more QALYs gained and 0.201 evLYGs from the health care system perspective. Slightly less than half (47%) of the QALY gain is from improvements in utility and 53% of the QALY gain is from an extension in survival. Similarly, from the modified societal perspective, patients treated with aducanumab resulted in slightly fewer incremental costs ($202,000) over the lifetime time horizon, and 0.159 QALYs gained and 0.215 evLYGs. Although the magnitude of costs is much higher in the societal perspective, reflective of the large caregiver impact often experienced with AD, the incremental results were similar across perspectives.

Table 4.3. Results for the Base Case for Aducanumab Compared to Supportive Care

Health Care System Perspective						
Treatment	**Drug Cost***	**Total Cost**	**QALYs**	**evLYs**	**Life Years**	**Life Years in Community**
Aducanumab	$199,000	$546,000	3.467	3.513	5.969	3.789
Supportive Care	$0	$342,000	3.313	3.313	5.827	3.628
Incremental	$199,000	$204,000	0.154	0.201	0.143	0.161
Modified Societal Perspective						
Treatment	**Drug Cost***	**Total Cost**	**QALYs**	**evLYs**	**Life Years**	**Life Years in Community**
Aducanumab	$199,000	$838,000	3.097	3.154	5.969	3.789
Supportive Care	$0	$636,000	2.938	2.938	5.827	3.628
Incremental	$199,000	$202,000	0.159	0.215	0.143	0.161

evLY: equal value of life years, QALY: quality-adjusted life year

*Includes acquisition cost and 6% mark-up.

Table 4.4 presents the incremental cost-effectiveness ratios from the base-case analysis, which includes estimates for the incremental cost per QALY gained, incremental cost per evLYG, incremental cost per life year gained, and incremental cost per additional year in the community. The incremental cost per QALY gained is approximately $1.33 million from the health care system perspective and $1.27 million from the societal perspective. The incremental cost per evLYG is approximately $1.02 million from the health care system perspective and $938,000 from the modified societal perspective.

Table 4.4. Incremental Cost-Effectiveness Ratios for the Base Case

Health Care System Perspective					
Treatment	**Comparator**	**Cost per QALY Gained**	**Cost per evLYG**	**Cost per Life Year Gained**	**Cost per Additional Year in the Community**
Aducanumab	Supportive care	$1,330,000	$1,020,000	$1,430,000	$1,270,000
Modified Societal Perspective					
Treatment	**Comparator**	**Cost per QALY Gained**	**Cost per evLYG**	**Cost per Life Year Gained**	**Cost per Additional Year in the Community**
Aducanumab	Supportive care	$1,270,000	$938,000	$1,420,000	$1,260,000

evLYG: equal value of life years gained, QALY: quality-adjusted life year

Threshold Analyses

Threshold analyses were conducted to identify at what aducanumab annual cost would certain cost-effectiveness thresholds be met. Tables 4.5 and 4.6 present the findings from these threshold analyses from both the health care system and modified societal perspectives, respectively.

Table 4.5. Threshold Analysis Results: Health Care System Perspective

	Annual Price*	**Annual Net Price**	**Annual Price to Achieve $50,000 per QALY**	**Annual Price to Achieve $100,000 per QALY**	**Annual Price to Achieve $150,000 per QALY**	**Annual Price to Achieve $200,000 per QALY**
Aducanumab	$56,000	N/A	$790	$2,950	$5,110	$7,260
	Annual Price*	**Annual Net Price**	**Annual Price to Achieve $50,000 per evLYG**	**Annual Price to Achieve $100,000 per evLYG**	**Annual Price to Achieve $150,000 per evLYG**	**Annual Price to Achieve $200,000 per evLYG**
Aducanumab	$56,000	N/A	$1,450	$4,260	$7,090	$9,900

evLYG: equal value of life years gained, N/A: not available, QALY: quality-adjusted life year

*The prices presented in this table are not inclusive of the 6% mark-up. The model adds a 6% mark-up to these annual prices.

Table 4.6. Threshold Analysis Results: Modified Societal Perspective

	Annual Price*	**Annual Net Price**	**Annual Price to Achieve $50,000 per QALY**	**Annual Price to Achieve $100,000 per QALY**	**Annual Price to Achieve $150,000 per QALY**	**Annual Price to Achieve $200,000 per QALY**
Aducanumab	$56,000	N/A	$1,510	$3,740	$5,960	$8,190
	Annual Price*	**Annual Net Price**	**Annual Price to Achieve $50,000 per evLYG**	**Annual Price to Achieve $100,000 per evLYG**	**Annual Price to Achieve $150,000 per evLYG**	**Annual Price to Achieve $200,000 per evLYG**
Aducanumab	$56,000	N/A	$2,310	$5,330	$8,360	$11,380

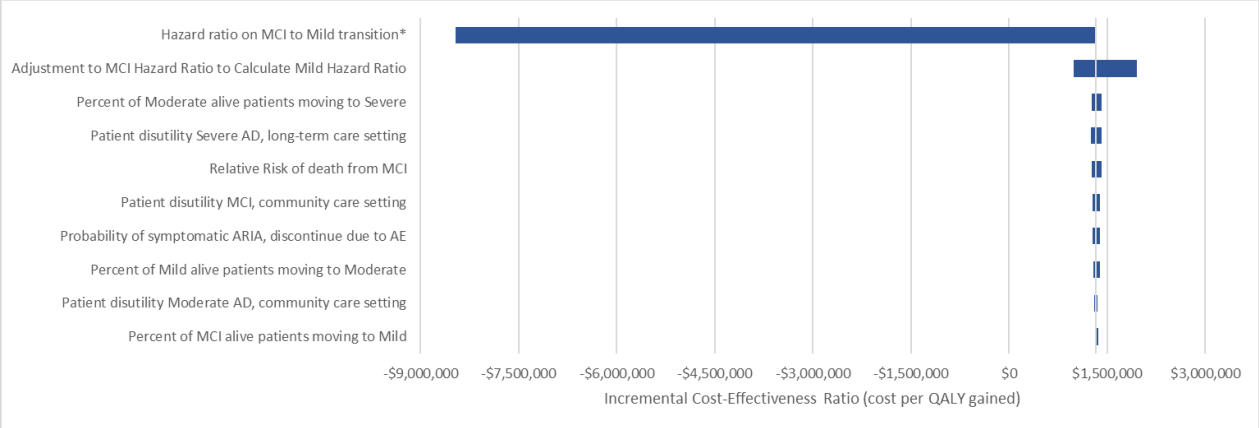
evLYG: equal value of life years gained, N/A: not available, QALY: quality-adjusted life year

*The prices presented in this table are not inclusive of the 6% mark-up. The model adds a 6% mark-up to these annual prices.

Sensitivity Analyses

To demonstrate the effects of uncertainty on both costs and health outcomes, we varied input parameters using available measures of parameter uncertainty (i.e., standard errors where available or reasonable ranges) to evaluate changes in findings. Figure 4.2 presents the results from a one-way sensitivity analysis from the health care system perspective. Notably, the most influential inputs on the findings are the effectiveness of aducanumab on delaying progression of AD as measured by a hazard ratio applied to the transition from MCI to mild AD as well as the adjustment to the hazard ratio on MCI to mild to calculate the hazard ratio for the mild AD health state progressions. Supplement Table E20 presents the inputs and results for each input that appeared in the tornado diagram from the health care system perspective.

Figure 4.2. Tornado Diagram, Health Care System Perspective†



AD: Alzheimer's disease, AE: adverse event, ARIA: amyloid-related imagining abnormality, MCI: mild cognitive impairment, QALY: quality-adjusted life year

*Upper bound of hazard ratio on MCI to mild transition is greater than 1 and thus generates a negative (more costly and less effective) incremental cost-effectiveness ratio. Lower bound of hazard ratio on MCI to mild transition is more favorable than the input used in the base case, and thus a more favorable cost-effectiveness estimate ($633,000) than the base-case analysis is generated.

A probabilistic sensitivity analysis was conducted to vary all inputs with noted uncertainty simultaneously. The price of aducanumab was not varied in sensitivity analyses because the uncertainty in price was separately accounted for in the threshold analyses. Tables 4.7 and 4.8 present the percent of the 1,000 iterations that were beneath thresholds of $50,000, $100,000, $150,000, and $200,000 per QALY gained and evLYG. Notably, no iterations were beneath these thresholds from either the health care system or the societal perspective. Dominated (i.e., more costly, less effective) incremental cost-effectiveness ratios that resulted in a negative incremental cost-effectiveness ratio were not considered beneath these thresholds. Additional results from the probabilistic sensitivity analyses can be found in Supplement Table E21 and Supplement Figures E1 and E2.

Table 4.7. Probabilistic Sensitivity Analysis Cost per QALY Gained Results

	Cost Effective at $50,000 per QALY	Cost Effective at $100,000 per QALY	Cost Effective at $150,000 per QALY	Cost Effective at $200,000 per QALY
Aducanumab vs. Supportive Care	0%	0%	0%	0%

QALY: quality-adjusted life year

Table 4.8. Probabilistic Sensitivity Analysis Cost Per evLYG Results

	Cost Effective at $50,000 per evLYG	Cost Effective at $100,000 per evLYG	Cost Effective at $150,000 per evLYG	Cost Effective at $200,000 per evLYG
Aducanumab vs. Supportive Care	0%	0%	0%	0%

evLYG: equal value of life years gained

Scenario Analyses

Given the insufficiency of the current evidence for aducanumab, and the large variation in cost effectiveness resulting from various plausible inputs for the treatment benefits for aducanumab, we conducted numerous scenario analyses to highlight the uncertainty and potential variation in the findings. Further, we evaluated the influence of different structural assumptions on the findings. We present here an optimistic treatment benefit scenario and a conservative treatment benefit scenario. These are not meant to represent the extremes of optimistic and conservative scenarios, but rather those that seem potentially plausible. Also, with regard to conservative scenarios, we did not explicitly model a scenario assuming no benefits to aducanumab (i.e., the hazard ratio from ENGAGE), as an economic model is not needed for an ineffective therapy.

In the optimistic treatment benefit scenario, we assumed the hazard ratio for EMERGE was the effectiveness for aducanumab (i.e., we did not blend this hazard ratio with ENGAGE) and we assumed the hazard ratio for EMERGE that was measured from the MCI to mild health state transition was also applicable to the mild to moderate AD health state transition (i.e., no reduction in effectiveness in the mild AD health state transition to moderate AD). Table 4.9 presents the cost-effectiveness estimates for this optimistic treatment benefit scenario.

In the conservative treatment benefit scenario, we continued to assume the blended hazard ratio from the EMERGE and ENGAGE trials for transitions from the MCI health state but assumed there was no effectiveness of aducanumab at reducing disease progression on transitions out of the mild AD health state because we only have hazard ratio data that has observed the transitions out of the MCI health state. Table 4.10 presents the cost-effectiveness estimates for this conservative treatment benefit scenario.

Table 4.9. Incremental Results from Optimistic Treatment Benefit Scenario Analysis

Health Care System Perspective					
Treatment	**Comparator**	**Cost per QALY Gained**	**Cost per evLYG**	**Cost per Life Year Gained**	**Cost per Additional Year in Community**
Aducanumab	Supportive care	$454,000	$360,000	$497,000	$438,000
Modified Societal Perspective					
Treatment	**Comparator**	**Cost per QALY Gained**	**Cost per evLYG**	**Cost per Life Year Gained**	**Cost per Additional Year in Community**
Aducanumab	Supportive care	$431,000	$329,000	$485,000	$428,000

evLYG: equal value of life years gained, QALY: quality-adjusted life year

Table 4.10. Incremental Results from Conservative Treatment Benefit Scenario Analysis

Health Care System Perspective					
Treatment	**Comparator**	**Cost per QALY Gained**	**Cost per evLYG**	**Cost per Life Year Gained**	**Cost per Additional Year in Community**
Aducanumab	Supportive care	$1,960,000	$1,490,000	$2,060,000	$1,850,000
Modified Societal Perspective					
Treatment	**Comparator**	**Cost per QALY Gained**	**Cost per evLYG**	**Cost per Life Year Gained**	**Cost per Additional Year in Community**
Aducanumab	Supportive care	$1,860,000	$1,360,000	$2,030,000	$1,830,000

evLYG: equal value of life years gained, QALY: quality-adjusted life year

Other scenarios are presented in the Supplement.

Uncertainty and Controversies

There were important uncertainties relevant to generating model outcomes, most of which related to the effectiveness of aducanumab. As emphasized in Section 3, the evidence on the effectiveness of aducanumab is inconsistent between the two pivotal trials. Our base-case analysis used a blend of the evidence from these two trials and required a treatment benefit assumption. We remain uncertain as to whether this averaged point estimate represents the true effect of aducanumab. Additional evidence on the effectiveness of aducanumab is needed to refine the effectiveness used in the model. Effectiveness is a primary driver of these cost-effectiveness findings, and thus wide uncertainty in aducanumab's effectiveness leads to wide uncertainty in its cost effectiveness.

Similarly, the evidence on aducanumab's effect on health state transitions is limited. The manufacturer provided the hazard ratio from the EMERGE trial for the MCI to mild AD health state transition. We did not receive the hazard ratio from the ENGAGE trial for the MCI to mild AD health state transition and thus had to assume an equivalence to the change in CDR-SB for the ENGAGE trial. There is scant evidence on transitions from other health states (e.g., transitions from mild AD or moderate AD), and thus assumptions were made. Additional evidence on these later disease transitions is necessary to further reduce uncertainty in the cost effectiveness. In addition to uncertainty in the effect of aducanumab on the progression of disease, there are other inputs in the

model that have uncertainty. For example, the utilities for the patient and caregiver are from cross-sectional studies. Limitations of these studies include representing cross-sectional utility weights to estimate impacts of an individual's health state changes over time and using instruments that might not be sensitive enough to detect AD-specific effects and/or second order effects for the caregivers. We have conducted extensive sensitivity and scenario analyses, although there may be uncertainty outside of what was modeled.

We presented an optimistic treatment benefit scenario and a conservative treatment benefit scenario based on currently available efficacy evidence for aducanumab. Even in our optimistic treatment benefit scenario, aducanumab exceeded commonly-cited thresholds. Potential AD treatments can generate favorable cost-effectiveness estimates at a high annual price, but the effectiveness would need to be greater than the most optimistic treatment benefit evidence for aducanumab. Using a similar modeling approach as our approach to modeling aducanumab, a treatment assumed to have no known harms that could maintain all patients in MCI for the rest of their lives would result in threshold pricing of up to $50,000-$70,000 per year based on commonly-cited thresholds.

Finally, some commentators have suggested that thresholds should be adjusted for disease severity.[42] Their work suggests a threshold higher than $100,000 to $150,000 per QALY gained for severe conditions (like AD). However, thresholds much lower than $100,000 to $150,000 per QALY gained are suggested for less severe conditions. Specific methods by which to assign lower thresholds to some conditions and higher thresholds to others have not gained consensus in health economics, in part because they require a view of a single societal value for severity, and also because any divergence in thresholds creates "winners and losers," with equal health gains for some patients viewed as worth "less" than those of others. We present results at multiple cost-effectiveness thresholds but continue to provide a base-case focus on results between $100,000-$150,000 per evLYG and per added QALY.

4.4 Summary and Comment

Our analyses suggest that the price of aducanumab is not in reasonable alignment with its clinical benefits, even under a scenario with optimistic assumptions regarding treatment effectiveness.

We presented the modified societal perspective as a co-base-case analysis in this report due to the large impact of AD on caregivers, represented in the model by a disutility for caregivers and a large loss of caregiver productivity outside of the health care system. However, the cost effectiveness of aducanumab in the modified societal perspective did not greatly differ from analyses performed using the health care system perspective. This result may seem counterintuitive, but is largely the result of the very small estimated impact of aducanumab on the progression to moderate and severe AD. In addition, keeping a patient in earlier AD states longer, which delays the transition to long-term care, can increase productivity losses for the caregiver. These countervailing factors

reduce the spread between the cost-effectiveness results using the health care system and modified societal perspectives. This highlights the complexities of capturing caregiver perspectives in the modified societal perspective in that caregivers may prefer to keep loved ones at home, rather than in a long-term care facility, although doing so may increase the negative financial impact on the caregiver.

The cost-effectiveness findings are primarily driven by the effectiveness of aducanumab. The uncertainty in the effectiveness of aducanumab percolates through to a wide range in potential cost-effectiveness estimates for aducanumab, ranging from dominated (more costly and less effective than supportive care) when aducanumab is not effective (as suggested by the ENGAGE trial) to estimates of around $350,000 per evLYG if aducanumab effectiveness is in alignment with optimistic treatment benefits assumed from the EMERGE trial.

5. Potential Other Benefits and Contextual Considerations

Our reviews seek to provide information on potential other benefits offered by the intervention to the individual patient, caregivers, the delivery system, other patients, or the public that was not available in the evidence base nor could be adequately estimated within the cost-effectiveness model. These elements are listed in the tables below and on the following page, with related information gathered from patients and other stakeholders. Following the public deliberation on this report, the appraisal committee will vote on the degree to which each of these factors should affect overall judgments of long-term value for money of the intervention in this review.

Table 5.1. Contextual Considerations

Contextual Consideration	Relevant Information
Acuity of need for treatment of individual patients based on the severity of the condition being treated	The acuity of need for treatment is high. There is currently only one potentially disease-modifying therapy for AD.
Magnitude of the lifetime impact on individual patients of the condition being treated	AD has a moderate lifetime impact on individual patients. Delaying or stopping progression of AD would improve the quality and, potentially, the length of life of patients. However, late-onset AD affects patients over the age of 65 and early-onset AD affects only a minority of patients. Thus, unlike diseases that impact the patient's entire lifespan, AD has a large effect on a portion of a patient's lifespan, leading to our assessment of moderate impact.

AD: Alzheimer's disease, MCI: mild cognitive impairment

Table 5.2. Potential Other Benefits or Disadvantages

Potential Other Benefit or Disadvantage	Relevant Information
Patients' ability to achieve major life goals related to education, work, or family life	AD has a substantial impact on patient independence for activities of daily living such as driving, shopping, financial tasks, etc. While most patients develop AD later in life after they have completed their education and left the workforce, delaying progression of the disease may have a significant impact on family life.
Caregivers' quality of life and/or ability to achieve major life goals related to education, work, or family life	Delaying progression of AD with aducanumab could potentially decrease caregiver impact and stress, increasing caregiver ability to achieve major life goals. Caregivers tend to be younger than patients, and thus the magnitude of benefit to caregivers may be larger over the lifetime than for patients.
Society's goal of reducing health inequities	The impact of aducanumab on health inequities is unclear. Underrepresented minorities such as Black and Hispanic populations have a higher prevalence of disease and are diagnosed at later stages, thus an effective treatment could decrease disparities. Additionally, an effective disease-modifying drug could raise awareness of the disease and increase early-stage diagnosis of the disease. However, such groups were not well represented in the clinical trials of aducanumab, and the drug was not tested in patients with moderate or severe AD, thus whether the drug has a differential impact in minority populations is not known.

AD: Alzheimer's disease, IV: intravenous, MCI: mild cognitive impairment

CTAF Votes

At the public meeting, CTAF deliberated and voted on the relevance of specific potential other benefits and contextual considerations on judgments of value for the interventions under review. The results of the voting are shown below. Further details on the intent of these votes to help provide a comprehensive view on long-term value for money are provided in the ICER Value Assessment Framework.

When making judgments of overall long-term value for money, what is the relative priority that should be given to *any* effective treatment for Alzheimer's disease, on the basis of the following contextual considerations:

Contextual Consideration	Very Low Priority	Low Priority	Average Priority	High Priority	Very High Priority
Acuity of need for treatment of individual patients based on the severity of the condition being treated	0	0	1	2	12
Magnitude of the lifetime impact on individual patients of the condition being treated	0	0	0	3	12

A majority of CTAF voted that the acuity of need for an AD treatment represents a very high priority. Currently, there is only one potentially disease-modifying therapy for AD. Prior to the approval of aducanumab, between 2002 and 2021, no new drugs were approved for the treatment of AD.

CTAF also voted that based on the magnitude of the lifetime impact of AD, very high priority should be given to an effective treatment. As noted, delaying or halting progression of AD would substantially improve the quality and, possibly, the length of life of patients.

What are the relative effects of aducanumab plus supportive care versus supportive care alone on the following outcomes that inform judgment of the overall long-term value for money of aducanumab?

Potential Other Benefit or Disadvantage	Major Negative Effect	Minor Negative Effect	No Difference	Minor Positive Effect	Major Positive Effect
Patients' ability to achieve major life goals related to education, work, or family life	2	7	6	0	0
Caregivers' quality of life and/or ability to achieve major life goals related to education, work, or family life	3	7	4	0	0
Society's goal of reducing health inequities	9	4	1	1	0

CTAF was split on whether aducanumab would have a negative effect or make no difference on a patient's ability to achieve life goals. In both cases, the votes were driven by the unanimous determination that the evidence is inadequate to demonstrate that aducanumab is superior to supportive care. Based on similar reasoning, CTAF voted that aducanumab would either have a potential negative effect or make no difference in caregivers' ability to achieve major life goals.

Lastly, a majority of CTAF voted that aducanumab may have a major negative effect on reducing health inequities. Importantly, Black and Hispanic populations have a higher prevalence of disease yet out of 3,268 total participants in ENGAGE and EMERGE, just 19 were Black or African American and only 104 were Hispanic or Latino. Further, Black and Hispanic patients are less likely to be referred specialists,[43] which is especially important given the current shortage of neurologists. In addition, aducanumab is given as an IV infusion every four weeks, which may impact individuals who live in rural areas where academic medical centers are sparser and access to specialists is limited. Relatedly, it may be difficult for patients and their caregivers to travel to infusion centers and take time off from work and/or school. Lastly, the price of aducanumab and the various associated out-of-pocket costs (i.e., travel, amyloid PET, etc.) may have a significant impact on patients and families with limited financial resources.

6. Health-Benefit Price Benchmarks

The HBPB is defined as the price range that would achieve incremental cost-effectiveness ratios between $100,000 and $150,000 per QALY gained or per evLYG.

ICER modeled a potential price for aducanumab by combining results from the two contradictory Phase III randomized trials. HBPBs for the annual cost of aducanumab are presented in Table 6.1. If aducanumab were determined to have no net health benefit, we would not have a suggested price. Finally, the HBPBs for the annual cost of aducanumab based on the optimistic and conservative treatment benefit scenarios are presented in Table 6.2 and Table 6.3.

Table 6.1. Annual Health Benefit Price Benchmarks for Aducanumab

Health Care System Perspective	Annual Price*	Annual Price at $100,000 Threshold	Annual Price at $150,000 Threshold	Discount to Reach Threshold Prices
QALYs Gained	$56,000	$2,950	$5,110	91%-95%
evLYG	$56,000	$4,260	$7,090	87%-92%
Modified Societal Perspective	**Annual Price***	**Annual Price at $100,000 Threshold**	**Annual Price at $150,000 Threshold**	**Discount to Reach Threshold Prices**
QALYs Gained	$56,000	$3,740	$5,960	89%-93%
evLYG	$56,000	$5,330	$8,360	85%-90%

evLYG: equal value of life years gained, QALY: quality-adjusted life year

*The prices presented in this table are not inclusive of the 6% mark-up. The model adds a 6% mark-up to these annual prices.

Table 6.2. Annual Health Benefit Price Benchmarks for Aducanumab based on Optimistic Treatment Benefit Scenarios

Health Care System Perspective	Annual Price*	Annual Price at $100,000 Threshold	Annual Price at $150,000 Threshold	Discount to Reach Threshold Prices
QALYs Gained	$56,000	$11,000	$17,350	69-80%
evLYG	$56,000	$14,310	$22,320	60-74%
Modified Societal Perspective	**Annual Price***	**Annual Price at $100,000 Threshold**	**Annual Price at $150,000 Threshold**	**Discount to Reach Threshold Prices**
QALYs Gained	$56,000	$12,760	$19,290	66-77%
evLYG	$56,000	$16,810	$25,350	55-70%

evLYG: equal value of life years gained, QALY: quality-adjusted life year

*The prices presented in this table are not inclusive of the 6% mark-up. The model adds a 6% mark-up to these annual prices.

Table 6.3. Annual Health Benefit Price Benchmarks for Aducanumab based on Conservative Treatment Benefit Scenarios

Health Care System Perspective	Annual Price*	Annual Price at $100,000 Threshold	Annual Price at $150,000 Threshold	Discount to Reach Threshold Prices
QALYs Gained	$56,000	$1,650	$3,110	94-97%
evLYG	$56,000	$2,580	$4,500	92-95%
Modified Societal Perspective	**Annual Price***	**Annual Price at $100,000 Threshold**	**Annual Price at $150,000 Threshold**	**Discount to Reach Threshold Prices**
QALYs Gained	$56,000	$2,350	$3,880	93-96%
evLYG	$56,000	$3,470	$5,560	90-94%

evLYG: equal value of life years gained, QALY: quality-adjusted life year

*The prices presented in this table are not inclusive of the 6% mark-up. The model adds a 6% mark-up to these annual prices.

CTAF Votes

No value vote was taken at the public meeting because CTAF voted unanimously that the evidence is not adequate to demonstrate that aducanumab is superior to supportive care.

7. Potential Budget Impact

7.1. Overview of Key Assumptions

Results from the cost-effectiveness model were used to estimate the potential total budgetary impact of aducanumab for patients with MCI due to AD or mild AD. Note that we did not include patients with moderate or severe AD in the potential budget impact analyses. We used the annualized price of $56,000 per treated patient per year plus administrative costs and the three threshold prices (at $50,000, $100,000, and $150,000 per QALY) for aducanumab in our estimates of budget impact. Potential budget impact is defined as the total differential cost, calculated as differential health care costs (including drug costs) minus any offsets in these costs from averted health care events (assuming the health care system perspective). We provide supporting findings of the potential budget impact assuming the modified societal perspective given that this perspective was included as a co-base-case in the cost-effectiveness analysis. All costs were undiscounted and estimated over a five-year time horizon.

This budget impact analysis included the estimated number of individuals with MCI due to AD or mild AD in the US who would be eligible for treatment with aducanumab. An unpublished analysis has used this approach to derive an estimate of 1.4 million patients in the US eligible for AD treatment that targets beta-amyloid, based on 2019 data. A scenario consistent with the 1.4 million estimate begins with prevalent cases of MCI and mild AD in the US of 4.6 million.[44,45] From there, one could assume that 90% of prevalent cases present to a clinician with symptoms and of those, 55% are diagnosed. Of those presenting to a clinician and who are diagnosed as MCI, we assumed 61.5% are beta-amyloid positive to arrive at 1.4 million patients eligible for treatment that targets beta-amyloid.[46] We assumed that 20% of these 1.4 million patients would initiate treatment in each of the five years, or approximately 280,000 patients per year.

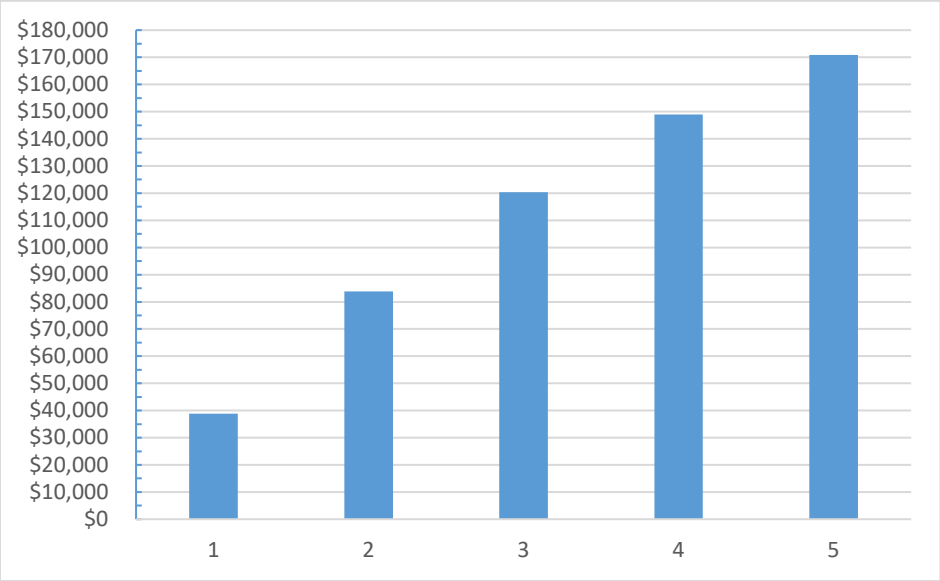
The aim of the potential budgetary impact analysis is to document the percentage of patients who could be treated at selected prices without crossing a potential budget impact threshold that is aligned with overall growth in the US economy. The five-year annualized potential budget impact threshold that should trigger policy actions to manage access and affordability is calculated to be approximately $819 million per year for new drugs. ICER's methods for estimating potential budget impact are described in detail in the Supplement Section F.

7.2. Results

Health Care System Perspective Results

Figure 7.1 illustrates the health care system perspective cumulative per-patient budget impact calculations for aducanumab compared to standard care, based on the annualized price of $56,000 per year of treatment. The average potential budgetary impact for aducanumab was approximately $39,600 per patient in year one, with the cumulative net cost increasing in years two through five as treatment continues, reaching approximately $176,200 by the end of the five-year horizon. The annual net cost was relatively consistent through years one through four but decreased in year five to $35,200 given various factors including treatment discontinuation and cost offsets. Additional average total and average net costs are presented in Supplement Table F1.

Figure 7.1. Cumulative Net Cost Per Patient Treated with Aducanumab for Five Years at Annual Price of $56,000 per Year*

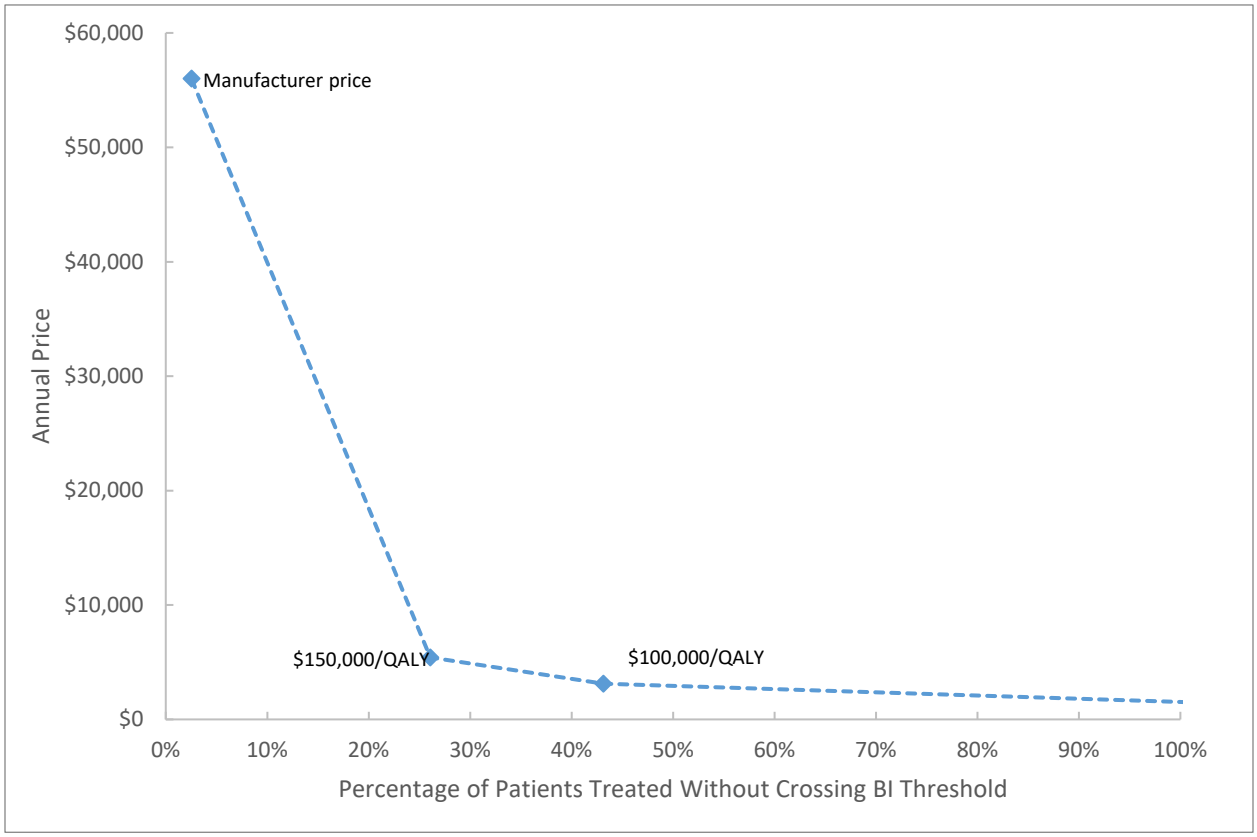


*Annual price of $56,000 per year does not include administration or mark-up costs that were modeled for estimating budget impact. First year aducanumab treatment and administration cost was $38,000 due to variable dosing in year one and due to discontinuation of the treatment.

Figure 7.2 illustrates the health care system perspective potential budget impact of aducanumab treatment of the MCI due to AD or mild AD population, based on the annualized price ($56,000 per year of treatment), and the prices to reach $150,000, $100,000, and $50,000 per QALY (approximately $5,110, $2,950, and $790 per year of treatment, respectively) compared to the usual care comparator. Approximately 2.5% of the roughly 280,000 patients could be treated each year without crossing the ICER budget impact threshold of $819 million per year over five years at the annualized price of $56,000 per year. Approximately 26% of patients could be treated each

year without crossing the budget impact threshold at the $150,000 per QALY threshold price, increasing to approximately 43% of the population at the $100,000 per QALY threshold price. All MCI and mild AD patients could be treated at the $50,000 per QALY threshold price, reaching 80% of the potential budget impact threshold.

Figure 7.2. Potential Budgetary Impact of Aducanumab Treatment (Health Care System Perspective)



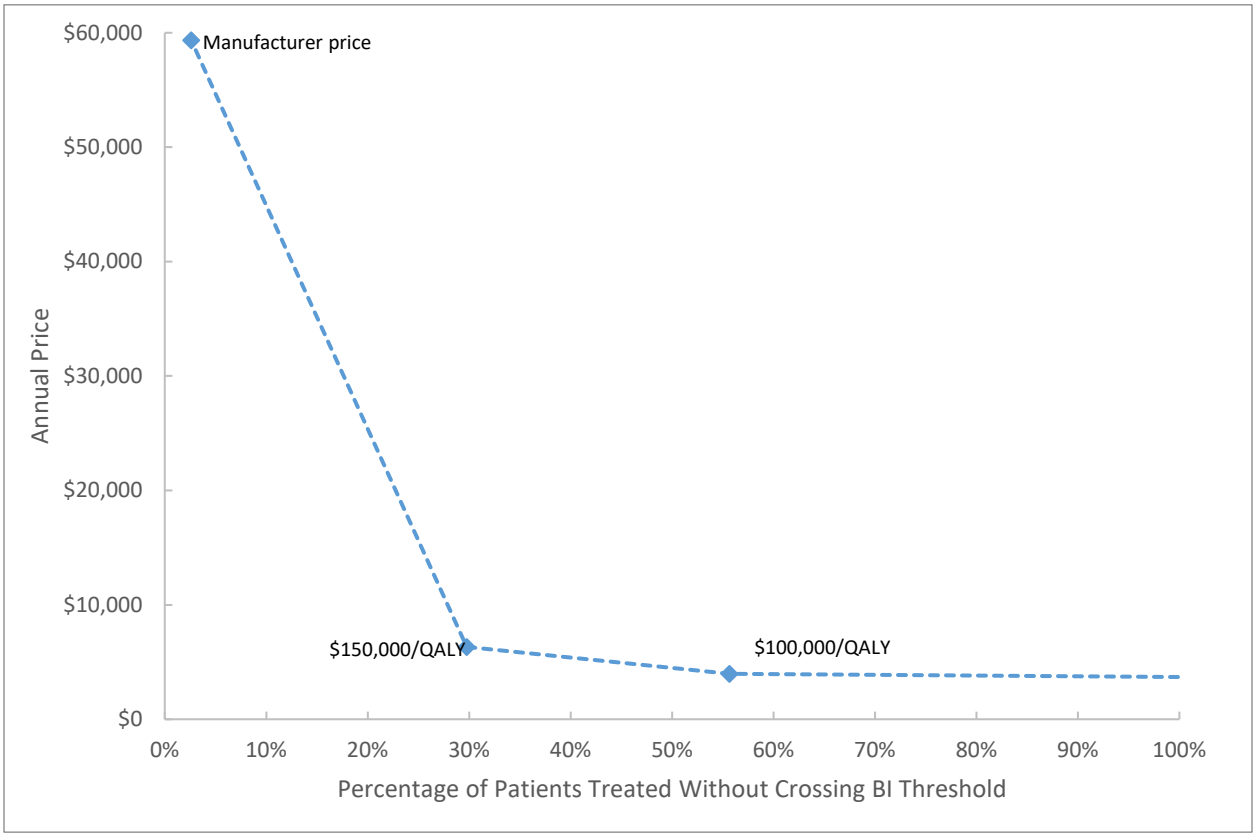
BI: budget impact, QALY: quality-adjusted life year

Modified Societal Perspective Results

Figure 7.3 illustrates the modified societal perspective potential budget impact of aducanumab treatment of the MCI due to AD or mild AD eligible population, based on the annualized price ($56,000 per year of treatment), and the prices to reach $150,000, $100,000, and $50,000 per QALY (approximately $5,960, $3,740, and $1,510 per year of treatment, respectively) compared to the usual care comparator. Approximately 2.6% of the roughly 280,000 eligible patients could be treated each year without crossing the ICER budget impact threshold of $819 million per year over five years at the annualized price of $56,000 per year. Approximately 30% of patients could be treated each year without crossing the budget impact threshold at the $150,000 per QALY threshold price, increasing to approximately 56% of the population at the $100,000 per QALY threshold price. All MCI and mild AD patients could be treated at the $50,000 per QALY threshold

price, reaching 23% of the potential budget impact threshold assuming the modified societal perspective.

Figure 7.3. Potential Budgetary Impact of Aducanumab Treatment (Modified Societal Perspective)



BI: budget impact, QALY: quality-adjusted life year

Access and Affordability Alert

Approximately 2.5%, or 35,000 out of 1.4 million AD patients eligible for treatment with aducanumab could be treated within five years before crossing the ICER potential budget impact threshold of $819 million per year when taking a health care system perspective. When taking a modified societal perspective, approximately 2.6% of the patients eligible for the treatment with aducanumab could be treated, which equates to roughly 36,000 individuals within five years. Testimony from clinical experts at the public meeting suggested a wide range of clinical uptake of aducanumab, with the majority suggesting numbers at or above 100,000 patients over five years or less. Therefore, at current pricing and projected uptake, the short-term potential budget impact exceeds ICER's threshold. Thus, ICER is issuing an access and affordability alert for aducanumab.

The purpose of an ICER access and affordability alert is to signal to stakeholders and policy makers that the amount of added health care costs associated with a new service may be difficult for the health system to absorb over the short term without displacing other needed services, creating

pressure on payers to sharply restrict access, or causing rapid growth in health care insurance costs that would threaten sustainable access to high-value care for all patients.

8. Policy Recommendations

Following its deliberation on the evidence, CTAF engaged in a moderated discussion with a policy roundtable about how best to apply the evidence on the use of aducanumab. The policy roundtable members included two patient advocates, three clinical experts, two payers, and one representative from the manufacturer. The discussion reflected multiple perspectives and opinions, and therefore, none of the statements below should be taken as a consensus view held by all participants.

Multiple Stakeholders

To prevent patients and families from being misled, patient groups, the manufacturer, and clinicians should accurately characterize the potential benefits of aducanumab as a slowing of decline of cognition and function and avoid using terms such as "improvement" or "return of quality of life" in all personal statements and advertising.

- Messaging from the manufacturer and patient groups, such as in patient-oriented websites and advertisements, should make it clear both that aducanumab has not been shown to improve cognitive and functional outcomes—rather it may slow decline—and also that removal of amyloid has not been conclusively demonstrated to affect clinical outcomes. For this last reason, all stakeholders should avoid using the term "amyloid-busting" in reference to aducanumab since that term would easily be interpreted by patients and families as confirmation that removal of amyloid has demonstrated clinical benefits.

- Clinicians and their patients should engage in shared decision-making founded upon a robust discussion of the potential harms and benefits of treatment. This should include discussion about the uncertain clinical significance of the results from EMERGE, uncertainty about whether removal of amyloid affects clinical outcomes, uncertainty about long-term harms, lack of benefit in moderate-to-severe AD, and potential financial toxicity. Many patients will have contraindications to therapy or a combination of comorbidities that should lead to very careful consideration of the risks and potential benefits for the individual. One common contraindication to therapy will be active use of anticoagulant medication, and patients and caregivers may be tempted to stop anticoagulation therapy in order to receive treatment with aducanumab; however, the safety and long-term outcomes of stopping anticoagulation must be weighed carefully for each individual patient.

Whether aducanumab is widely prescribed or not, health systems, manufacturers, payers, and the FDA should take steps now that will reduce disparities and improve equitable access to dementia diagnosis, management, and future new therapies.

AD is underdiagnosed and often poorly managed in the US. Studies consistently demonstrate that quality of care for patients with AD is poorer than that for other chronic diseases,[47] in part due to underuse of effective supportive care programs, lack of integration of community-based programs into the health care system, shortage of dementia care expertise in rural areas, and lack of time for effective coordination of care, particularly in primary care settings. With aducanumab now approved for treatment, the capacity of the US health care system will prove an ongoing limitation to early diagnosis and consideration of treatment.

Additionally, there are significant racial and ethnic disparities in AD diagnosis and management. Black and Hispanic Americans are 1.5 to two times more likely to have AD,[8] and individuals with limited English proficiency and persons with low education levels are also more likely to be underdiagnosed and live longer with cognitive dysfunction.[48]

To address these concerns, health systems should take the following actions:

- **Invest resources to increase capacity for screening and diagnosis**. Whether aducanumab is viewed as an effective treatment or not, improved access for screening and diagnosis across all segments of the patient population is an important goal to reduce existing disparities in dementia care. Actions to reduce disparities could include increasing access to dementia specialists in all communities through outreach clinics and telehealth; improving training, time support, and reimbursement for screening and diagnosis to be done in non-specialist settings (e.g., primary care); and supporting development of newer diagnostic testing such as blood-based biomarkers.
- **Implement evidence-based supportive care models such as the Alzheimer's and Dementia Care Program[49] for all AD patients.**
- **Ensure that all interventions are appropriate for culturally and linguistically diverse populations and that interventions are accessible to low literacy populations**. Such populations, due to social, economic, and cultural differences, may have different perceptions of illness and different goals of care.[50]

The manufacturer should take the following actions:

- **Work with communities and patient groups to develop reliable methods for recruiting diverse populations for clinical trials and promote retention of such populations**. Out of 3,268 patients enrolled in ENGAGE and EMERGE, 19 (0.6%) were Black and 49 (1.5%) were Hispanic. Lack of information about the potential differences in safety or effectiveness

across different patients undermines knowledge necessary for tailored personal care decisions.

- **Biogen should lower the price of aducanumab to a value-based price range determined by independent research to fairly align with demonstrated benefits for patients. Fair pricing is required to fulfill the social responsibility held by manufacturers to avoid financial toxicity that falls hardest on the most vulnerable patients**. Value-based pricing is one method of preserving access and affordability for new therapies. Drug prices that are set well beyond the cost-effectiveness range can not only cause direct financial toxicity to patients, but also contribute to general health care cost growth that pushes families out of the insurance pool and causes rationing of care that may be harmful. However, when treatments are first launched, which is when pricing and coverage decisions have to be made, the evidence on the long-term value of these treatments may be extremely limited. Fair pricing in the context of such uncertainty should favor a more conservative approach, with initial pricing erring on being more affordable.

Payers and policymakers should take the following action:

- **Work to achieve more equitable access to current and future therapies by changing benefit designs in Medicare and private insurance to reduce the maximum amount patients must pay out of pocket**. The out-of-pocket maximum for Part B services in Medicare is not capped, leading to a situation in which many patients will not be able to undertake certain treatments or will do so only with the guarantee of suffering significant financial hardship. Although many patients will carry supplemental insurance, close to six million Medicare beneficiaries do not, and millions more with Medicare Advantage have very high out-of-pocket maximums that they may not be able to afford. Oncology has been the primary example of this phenomenon, and it would be unconscionable should the advent of effective treatments for AD be accompanied by the extension of this same dysfunctional system. Lower out-of-pocket requirements obviously have broader financial repercussions on Medicare premiums and sustainability, and should be linked conceptually, and perhaps legislatively, with requirements for value-based pricing for infused agents.

The FDA should take the following action:

- **Incorporate specific targets for pivotal trials to ensure that patients enrolled adequately reflect the population of patients with the condition in the US.**

Payers

Payers should evaluate coverage of aducanumab in the context of the evolving evidence on its benefits and harms. Based on current evidence and the inadequately justified elevation of amyloid clearance into the role of surrogate outcome, it is not unreasonable for payers to deny coverage for aducanumab as lacking evidence to support that it is medically necessary, pending additional data.

Given the known risks and uncertain effectiveness of aducanumab, it is not inherently unethical for health plans to deny coverage. Importantly, non-coverage in this context should not be viewed as contributing to greater disparities in care just because very wealthy individuals would still be able to access the treatment by paying for it completely out of pocket.

Payers who do choose to provide insurance coverage for aducanumab should cover appropriate diagnostic testing for amyloid in the brain.

Perspectives on specific elements of cost sharing and coverage criteria within insurance coverage policy are discussed below.

Coverage Criteria

- **Age**: Patients aged 50 to 85 were eligible for the two pivotal trials of aducanumab and many payers are likely to adopt this age range as a part of formal insurance coverage criteria. However, consideration should be given to including patients age <50 who may have early-onset AD and who otherwise meet eligibility criteria.
- **Patient eligibility**: The updated FDA label states that "ADUHELM is an amyloid beta-directed antibody indicated for the treatment of Alzheimer's disease. Treatment with ADUHELM should be initiated in patients with mild cognitive impairment or mild dementia stage of disease, the population in which treatment was initiated in clinical trials." Payers are very likely to create specific language to define the terms in the FDA label in order to produce a narrow focus of coverage given the risks of treatment, the uncertainty of benefit, and the potentially very large patient population.
    - **MCI or mild dementia**: Payers are likely to require documentation of cognitive decline for some period of time, e.g., six to 12 months. There are multiple cognitive tests to distinguish the level of cognitive impairment. Clinical experts at the public meeting advised that the most practical validated tests are the MMSE, CDR-GS, and the Montreal Cognitive Assessment (MoCA). All of these tests are validated and were used as eligibility criteria within the pivotal trials.
        - MMSE score ≥24 (cutoffs for MCI and mild dementia for MMSE vary by study and by educational level. MMSE ≥24 was used as inclusion criteria for aducanumab clinical trials.[51])

        - CDR-GS score 0.5-1
        - MoCA score 19-24

    - **Determination of AD versus other causes of dementia**: To exclude other causes of dementia, payers are likely to require a screening MRI within the previous year that does not show evidence of acute or sub-acute hemorrhage or diffuse white matter disease. Although tests to demonstrate the presence of amyloid will be the next step in insurance coverage for most payers, some may also request that blood tests be done for other causes of dementia, including tests for syphilis, thyroid disease, and vitamin B12 deficiency.

      To establish amyloid presence in the brain, payers will have the choice of covering PET scans and/or CSF-based testing and may choose to cover one or both. Emerging blood tests for neuro-amyloid are not yet adequately validated for routine clinical use. If CSF-based testing is chosen, payers should be aware that lumbar puncture may be more technically difficult or contraindicated in older patients due to spinal degenerative disease.

      Although the clinical trials tested for ApoE4 gene status, current dosing protocols do not differentiate between ApoE4+ and ApoE4- patients, and while ApoE4+ patients are at higher risk of developing ARIA, there is no current expert recommendation about ApoE4 testing in this context.

    - **Exclusion criteria**: Given the narrow balance between potential benefit and harm for aducanumab, it is not unreasonable to use clinical trial criteria for exclusions. These criteria include:
        - History of stroke or transient ischemic attack or loss of consciousness in the past one year; clinically significant or unstable psychiatric illness within the last six months; history of significant cardiac disease (e.g., myocardial infarction, heart failure within last one year); impaired renal or liver function
        - Use of anti-platelet or anti-coagulant medications other than aspirin at a prophylactic dose
        - Contraindication to amyloid testing (e.g., PET, lumbar puncture) or to MRI brain scan (e.g., metallic implants).

- **Duration of coverage and renewal criteria**: Initial coverage will likely be for a period of six to 12 months, which is long enough for dose titration and potential assessment of side effects or progression to moderate dementia. The language in the FDA label does not formally exclude continuation of treatment for patients who progress to moderate dementia, but some payers are likely to institute a requirement that patients remain in the MCI or mild dementia levels of cognitive testing in order to receive continuation of

coverage. Although there are no data on the safety or effectiveness of aducanumab among patients with moderate dementia, some clinicians and patients who may feel that their course of illness has been slowed with treatment will object to any decision to deny continuation of coverage past the mild AD stage.

- **Provider restrictions**: Because of the narrow benefit/harm balance and the potential for severe side effects, initiation of aducanumab is best managed by specialists, or in consultation with specialists, who have the expertise to accurately diagnose and manage dementia. Relevant specialties include neurology or geriatrics.

Step Therapy

- There is no clinical rationale to justify requiring step therapy with available symptomatic drugs used for patients with AD.

Coverage Considerations Specific to Medicare

If Medicare chooses to provide coverage following its National Coverage Determination (NCD) process, it should work with input from the National Institutes of Health and other research methodology experts to design a rigorous Coverage with Evidence Development (CED) program requiring patients be enrolled in an RCT or a trial using a rigorous quasi-experimental "waitlist" research design.

Although non-coverage of aducanumab would not be unreasonable given the known harms of aducanumab and its uncertain benefits, it is more likely that the culmination of Medicare's NCD process will be approval of coverage. Under this scenario, it is vital that coverage be provided in a way that can speed the ability to gain additional data on the safety and effectiveness of aducanumab. Medicare should therefore explore how to implement a rigorous program for this agent should it be covered. Medicare should seek broad public comment and seek to partner with study design experts at the National Institutes of Health in order to develop an approach to CED for aducanumab that will allow for appropriate access in all communities while also being rigorous enough to answer the substantial remaining uncertainties regarding this treatment.

CED is most often implemented through observational study designs built upon patient registries, but Medicare should be aware of the difficulties in using this approach to answer the fundamental question about relative effectiveness that remains for aducanumab. The best way to answer this question scientifically would be another randomized trial, but patients may bristle at the idea of having a random chance of receiving the approved drug, and even cluster randomized designs may be viewed as politically unpalatable.

As an alternative, Medicare should consider formal "waitlist" designs. Given the significant limitations in the infrastructure for delivering infused aducanumab to a large number of patients in

the short term, a waitlist design study would gather baseline information on all patients qualifying for treatment and then randomize patients or treatment centers to early versus late administration. This quasi-experimental design allows patients to serve as their own controls while they are waiting for treatment and can produce rigorous evaluations of interventions rolled out over a number of months or years. Patients and families may find the idea of a waitlist design objectionable, but if the reality is that some patients will be forced to wait due to infrastructure limitations, it could prove more equitable to formalize a waitlist design and assign treatment in a fashion to assure that patients are not more likely to obtain early treatment on the basis of greater resources, preferential access networks, or geography, all of which may deepen health inequities. Consideration could be given to randomization within a waitlist design as a method of limiting potential bias. Patient advocacy groups, clinical specialty societies, and other stakeholders must all be closely engaged in examining the pros and cons of different options, but it seems imperative that patients, families, and the country find out whether aducanumab works through a rigorous study or set of studies that conclude far earlier than the nine years the FDA allowed Biogen to complete its confirmatory trial.

Regulatory

For AD, the FDA should act quickly to set a clearer regulatory framework in place by specifying a threshold range for amyloid clearance that will be accepted going forward as "reasonably likely" to provide patient benefit. More broadly, the FDA should take concrete steps to become clearer about the way it engages its advisory committees and to be transparent and consistent in its designation of surrogate outcomes and the timing of its decisions to use the accelerated approval pathway.

The approval process for aducanumab left public confidence in the FDA shaken. The FDA worked more closely with Biogen than usual to perform post-hoc analyses to try to understand the reason for the discrepant outcomes in the pivotal trials for aducanumab. An advisory panel was convened and was highly critical of the conclusions from these post-hoc analyses and voted against approval; after further deliberations at the FDA, however, the drug was approved, not on the basis of the FDA's interpretation of the clinical outcomes data, but by repurposing amyloid clearance into a surrogate endpoint that was now considered "reasonably likely" to lead to patient benefit. The FDA made this decision without disclosing any data showing patient-level correlation of amyloid clearance with cognitive outcomes from the trials of aducanumab. The FDA also made this decision despite the fact that the accelerated approval pathway was meant for drugs in areas of great need, which do not yet have data on patient-centered clinical outcomes, yet clinical outcome measures for AD do exist and are not difficult to measure in relatively short trials. Faced with discrepant trial data, the FDA found sudden confidence in an outcome that had been previously dismissed as a "reasonably likely" surrogate outcome, took a detour to accelerated approval, and thereby justified approval using an approach inconsistent with past FDA practice.

Nonetheless, going forward, the precedent for amyloid-clearing drugs has been set, and sponsors of these drugs may assume that it is not necessary to have outcomes data beyond amyloid clearance before applying for regulatory approval. Manufacturers of drugs that clear tau from the brain may assume the same approach will be taken with their drugs. To guide manufacturers, but also to create some semblance of transparency and consistency, the FDA should immediately act to define publicly what degree of amyloid reduction it will consider as a minimum to qualify a drug as "reasonably likely" to lead to clinical benefit.[52] Similarly, they should act now to present how they intend to approach setting thresholds for other potential "reasonably likely" surrogate outcomes as part of regulatory decisions for non-amyloid treatments of dementia. Will these be required to demonstrate improvements in clinical outcomes, putting them at a disadvantage compared to amyloid-decreasing agents? Will they be able to gain approval showing improvements in their own surrogate outcomes linked to their mechanism of action? The FDA should clarify these questions expeditiously in order to improve transparency and to start to rebuild the trust that has been lost through its torturous approval process for aducanumab.

The FDA should be loath to approve plans for manufacturers to combine Phase II and Phase III studies in order to ensure that correct dosing is being tested in adequate patient populations in Phase III trials.

One of the reasons proposed by Biogen that only the results of the EMERGE study should be viewed as definitive was the fact that this study had more patients whose treatment was affected by a dosing protocol change in the ApoE+ group (Protocol Version 4), allowing patients in this group to be titrated to the highest 10 mg/kg dose. Implementation of this protocol change during the course of both pivotal trials reflected the lack of understanding by the manufacturer of the optimal dosing strategy, something that is routinely gained through Phase II trials prior to commencing Phase III trials. In the case of aducanumab, the merging of Phase II and Phase III trials, combined with early discontinuation of both trials due to a pre-specified futility analysis, led to the need to perform post-hoc analyses to try to assess whether the protocol change might be a contributing factor in the disparate trial results. Post-hoc analyses are extremely vulnerable to bias and should not be the standard by which regulatory approvals are determined. The FDA should shift away from joint Phase II/III trials for future treatments of AD.

Manufacturer

Biogen should accelerate the timeline of a confirmatory RCT conducted internationally to provide more definitive evidence on the clinical efficacy of aducanumab as well as additional safety data.

In its approval of aducanumab via an accelerated pathway, the FDA required Biogen to complete a post-approval confirmatory RCT within nine years. Given the conflicting Phase III trial results, the current lack of definitive evidence that reduction in amyloid translates into slowing of cognitive decline, and the high price of aducanumab, it is imperative that Biogen seek to complete the

confirmation RCT as soon as possible. It is very likely that an adequate RCT will not be possible in the US following approval, therefore Biogen will need to perform this trial internationally where the drug is not available.

Clinicians and Clinical Societies

Clinicians and clinical specialty societies should bear witness to the unmet needs of patients and families with AD to support broad consideration of the value of emerging therapies. But all clinicians and specialty societies should also exercise their obligation to provide objective guidance on interpreting the uncertain data on aducanumab, and should advocate for fair pricing and for affordable and equitable access to all available treatments.

Professional organizations have a critical role to play in helping payers and other policymakers understand the need of patients for effective treatments for dementia. It is equally important that they advocate for affordable and equitable access to new therapies. Statements on aducanumab such as those from the American Academy of Neurology[53] and the American Geriatrics Society[54] expressing concern about the uncertainty of clinical benefits and the high cost of aducanumab are outstanding examples of the type of advocacy professional organizations should engage in during the debate about initial approval of and pricing of new therapies.

Patient Organizations

Patient organizations have a vital role to play to promote objective descriptions of the risks and benefits of new therapies in order to support shared decision-making for every patient. In addition, patient groups have a powerful voice and should apply it to create significant pressure for fair pricing and appropriate insurance coverage across all sectors of the health system.

Patient groups should endeavor to educate patients about the potential risks and benefits of new therapies, particularly those with the potential for substantial harms, and work with other stakeholders to develop and disseminate evidence-based, balanced materials that are accessible to all patients, including those with low health literacy. Patient groups should also accept responsibility to publicly promote access and fair pricing of new therapies. For example, the Alzheimer's Association made a statement following the announcement of aducanumab's price tag which included, "This price is simply unacceptable. For many, this price will pose an insurmountable barrier to access, it complicates and jeopardizes sustainable access to this treatment, and [it] may further deepen issues of health equity. We call on Biogen to change this price."[55] This statement is a strong example of the type of advocacy for fair pricing needed when pricing exceeds predicted value of a drug. Patient groups should additionally follow-up such statements with organized campaigns to advocate for fair pricing, for example, by encouraging patients and families to write to Congress or launch public relation campaigns with such messaging.

Future Research

Researchers should focus on finding ways to improve targeting of drugs to find patients who will derive the greatest benefit and decrease utilization in patients who have low probability of benefit and high risk for harm, particularly for diseases with heterogeneous populations and for therapies with narrow therapeutic windows.

For drugs such as aducanumab, where potential benefits are small and potential harms are great, understanding which subset of patients will benefit most and which are most likely to be harmed is critical to increasing the value of treatments and maintaining affordability. Thus, drug development should also be accompanied by robust research into novel diagnostic strategies (e.g., liquid-based amyloid screening tests, genetic markers) that have the potential to identify the target population more accurately, thus potentially lowering the cost of treatment and minimizing harm to patients.

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Report Supplement

A. Background: Supplemental Information

A1. Detailed Epidemiology of AD

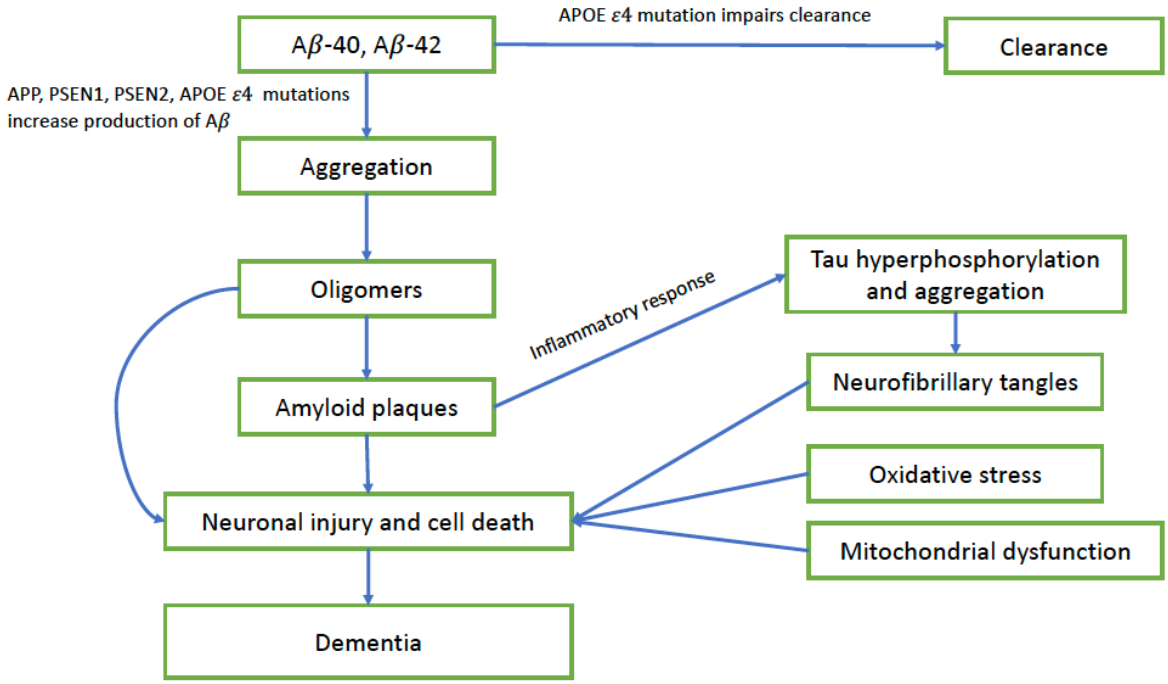
Sex differences: More women are living with AD than men; approximately 12% of women who are 65 and older in the US have AD, compared with 9% of men.[2] This is thought to be due to the longer life expectancy of women; however, other genetic and environmental factors may also have disproportionate influence based on sex. There is evidence that symptoms of the disease may manifest differently in women and men, particularly with respect to neuropsychiatric symptoms.[56] Women may be more likely to exhibit pacing/wandering symptoms, complain, hide or hoard things, and to experience anxiety, irritability, and possibly, delusions.

Racial/ethnic differences: Nearly twice as many Black Americans have AD, compared with non-Hispanic Whites (18% vs. 10%).[2] Hispanics also have a higher prevalence of AD compared with Whites 65 and older (14% vs. 10%), though this may differ between specific Hispanic groups. Asian Americans have the lowest incidence and prevalence of AD, though again there may be heterogeneity within specific Asian American subgroups.

A2. Amyloid Hypothesis of AD

The exact mechanisms by which neuronal loss occurs in AD have yet to be fully elucidated. The most commonly cited cause of AD is the so-called "amyloid hypothesis" (Figure A1).[1] This explanation of the pathophysiology of AD postulates that the aggregation of beta-amyloid oligomers in the brain leads to amyloid plaques, which in turn spark an inflammatory cascade that results in progressive synaptic and neuronal injury. They also trigger tau phosphorylation, resulting in neurofibrillary tangles, which in turn also cause neuronal injury. Oxidative stress and mitochondrial dysfunction also play a role in damaging neurons. These changes in the brain result in widespread neurodegeneration and cell death, and ultimately cause the clinical signs and symptoms of dementia.[57,58]

Figure A1. Amyloid Cascade Hypothesis of AD



Aβ: beta-amyloid, APOE ε4: apolipoprotein E4, APP: amyloid precursor protein, PSEN: presenilin

A3. Definitions

Alzheimer's disease (AD): A neurodegenerative brain disease with presenting symptoms including memory loss, decline in cognitive function, and language problems. The main pathologies of AD are the accumulation of two abnormal protein deposits: protein tau tangles inside neurons and beta-amyloid plaques outside of the neurons in the brain. AD progression can occur without noticeable changes to an individual. This progression of disease exists on a continuum with stages including preclinical AD, MCI due to AD, and dementia due to AD.[59]

Symptoms of AD include impairment in cognitive domains such as memory, language, executive function (e.g., problem-solving and completing tasks), and visuospatial function, which result in the loss of ability to perform activities of daily living (e.g., paying bills, bathing, dressing, etc.).[60,61] Changes in mood and personality, along with decreased or poor judgment and sleep disturbances, also occur. Treatment of AD focuses on symptom management as well as treatment of comorbid conditions that may be risk factors for worsening dementia (e.g., hypertension, diabetes, cardiovascular disease, smoking).[5,6] Additionally, avoidance of polypharmacy and elimination of non-essential medications that may impair cognition is essential.

Alzheimer's Disease Assessment Scale – Cognitive Subscale (13-Item Version) (ADAS-COG 13): A measure including completion of cognitive tasks, such as copying an image or identifying an object, and clinical ratings of certain cognitive performances. Scores on this scale range from 0 to 85 with a higher score meaning greater cognitive impairment.[25] The minimal clinically important difference in early AD is estimated to be 3 points.[62]

Alzheimer's Disease Cooperative Study – Activities of Daily Living Inventory (MCI Version) (ADCS-ADL-MCI): A measure including 18 items relating to everyday activities as reported by the caregiver. An individual's caregiver report changes in function state over a month's time with scores ranging from 0 to 53 with lower scores indicating decline in function.[25]

Amyloid-related imaging abnormalities (ARIA): These abnormalities can present as either edema/effusion (ARIA-E) or hemorrhage or superficial siderosis (ARIA-H). ARIA is commonly seen early on in a treatment period, is mostly asymptomatic, and more frequently observed in APOE ε4 carriers as compared to non-carriers. Management of ARIA in the context of the aducanumab clinical development program include MRI monitoring, dose suspension/termination, treatment titration, etc.[25]

Apolipoprotein E4 (APOE ε4): A gene that increases the risk of (but does not guarantee) an individual developing AD as compared to individuals who do not carry this gene. More research is recommended by the Alzheimer's Association to better understand the correlation between APOE ε4 carriers and the onset of AD.[59]

Clinical Dementia Rating – Sum of Boxes (CDR-SB): A measure of cognition and function in AD on a scale of 0 to 18 that can change in increments of 0.5 of higher. A higher score indicates greater disease severity. The measure includes three domains relating to cognition and three domains related to function including topics of memory, problem-solving, personal care, community engagement, etc.[25] The minimal clinically important difference in early AD is estimated to be 1-2 points.[26]

Disease-modifying therapy: Treatments or interventions that affect the underlying pathophysiology of a disease and have a beneficial outcome on the course of AD.[63]

Mini-Mental State Examination (MMSE): A measure of cognition that includes 11 tasks relating to topics of word recall, attention, language ability, etc. The scale ranges from 0 to 30 with a lower score reflecting greater cognitive impairment. Key limitations of this scale are its sensitivity to education level and practice effects and significant ceiling effects.[25] The minimal clinically important difference in AD is estimated to be 1-3 points, and in early AD to be 1-2 points.[24,26]

Neuropsychiatric Inventory-10 (NPI-10): A measure of 10 neuropsychiatric symptoms including delusions, euphoria, disinhibition, etc. The scale is administered by an interviewer who collects

information of the presence, frequency, and severity of the symptoms. Scores range from 0 to 120 with a higher score reflecting worse neuropsychiatric symptoms.[25]

A4. Potential Cost-Saving Measures in AD

ICER includes in its reports information on wasteful or lower-value services in the same clinical area that could be reduced or eliminated to create headroom in health care budgets for higher-value innovative services (for more information, see https://34eyj51jerf417itp82ufdoe-wpengine.netdna-ssl.com/wp-content/uploads/2021/03/ICER_2020_2023_VAF_013120-4-2.pdf). These services are ones that would not be directly affected by therapies for AD (e.g., delay in entry into long-term care), as these services will be captured in the economic model. Rather, we are seeking services used in the current management of AD beyond the potential offsets that arise from a new intervention. During stakeholder engagement and public comment periods, ICER encouraged all stakeholders to suggest services (including treatments and mechanisms of care) currently used for patients with AD that could be reduced, eliminated, or made more efficient. No suggestions were received.

B. Patient Perspectives: Supplemental Information

Methods

ICER engaged with patient groups, including representatives from AD advocacy organizations and caregiver organizations, and clinical experts to gather information to better understand patient and caregiver experiences with the disease. In total, we spoke with two advocacy organizations and one caregiver support organization via conference calls as well as with eight clinical experts throughout the review process. We also reviewed research literature suggested by or provided to ICER by advocacy organizations as well as data from qualitative interviews and surveys of AD patients and caregivers provided to us by Us Against Alzheimer's.[4,23]

Patient, caregiver, and advocacy groups provided information on the impact of AD on patients and caregivers throughout the disease course, particularly concerning aspects of the disease and caregiving that are not well-reflected in the current literature. These organizations also assisted with literature review to find information that was considered for inputs into the economic model.

C. Clinical Guidelines

Clinical practice guidelines for the treatment of MCI and mild AD have been issued by several US and non-US-based organizations. These guidelines are summarized below.

American Academy of Neurology[5]

In 2018, the American Academy of Neurology published guidelines for the management of MCI. The guidelines recommended that clinicians assess for MCI using validated tools, evaluate patients with MCI for modifiable risk factors, assess for functional impairment, assess for and treat behavioral symptoms, and consider discontinuing medications that may impair cognition. Furthermore, guidelines suggested that clinicians should counsel patients about the expected course of the disease, encourage long-term planning, and discuss the lack of effective medication options, including the lack of benefit of cholinesterase inhibitors on cognition and progression.

National Institute for Health and Care Excellence (NICE)[6]

Guidelines for the diagnosis and management of dementia were published in June 2018 by NICE in the United Kingdom. The guidelines include recommendations on involving people living with dementia in decisions about their care, assessment and diagnosis of dementia, interventions to promote cognition, independence and well-being, pharmaceutical interventions, managing non-cognitive symptoms, supporting caregivers, and staff training and education. Among the non-pharmacological interventions recommended were group cognitive stimulation and reminiscence therapy and cognitive rehabilitation, and recommendations against acupuncture, herbal supplements, vitamin E, and non-invasive brain stimulation. Consideration should be given to minimizing medications that may impair cognition. Acetylcholinesterase inhibitors were recommended for managing mild-to-moderate AD symptoms, and memantine and/or combination therapy was recommended for moderate-to-severe AD. Recommendations were also made to manage non-cognitive symptoms (e.g., behavioral symptoms, depression, sleep problems), and managing other long-term conditions common in patients with AD, such as pain, falls, and incontinence.

American Psychiatric Association[64]

The American Psychiatric Association published practice guidelines for the treatment of patients with AD in 2014. The guidelines discuss the evidence of efficacy for medications to treat AD, and state that based on the available evidence, memantine, cholinesterase inhibitors, or a combination of the drugs, may be used to treat AD. They also recommend using nonpharmacological interventions and environmental measures to reduce psychosis and agitation before considering use of antipsychotics based on the lack of evidence for efficacy of antipsychotics in this situation.

The guidelines also discuss the evidence for a variety of psychosocial interventions and alternative treatments, and offer guidance on managing caregiver stress.

The National Institute on Aging-Alzheimer's Association[60,61,65]

In 2011, the National Institute on Aging and the Alzheimer's Association convened a workgroup to revise the diagnostic criteria for MCI and AD. These included diagnostic criteria both to be used in the clinical setting and in research settings. Clinical and cognitive criteria were established to differentiate MCI and AD, and to establish the potential etiology of MCI. Furthermore, for AD, diagnostic criteria incorporating biomarkers were defined. Biomarkers to incorporate into research criteria were also discussed, including PET amyloid imaging for beta-amyloid deposition and CSF fluid tau/phosphorylated tau, among others.

In 2018, the National Institute on Aging and the Alzheimer's Association issued an updated research framework intended to guide observational and interventional research. The objective was to create a scheme for defining and staging AD across the lifespan. The framework establishes a biomarker-based system for classifying the neuropathologic changes seen in AD, including imaging and CSF biomarkers. Biomarkers are separated into those related to beta-amyloid plaques (e.g., CSF Aβ-42, amyloid PET), fibrillar tau (e.g., CSF phosphorylated tau, tau PET), and neurodegeneration or neuronal injury (e.g., anatomic MRI, total CSF tau). Categorization of AD- and non-AD-related pathologic change using biomarkers is discussed. Additionally, the document discusses cognitive staging applicable to research cohorts, including syndromal categorical cognitive staging that uses traditional syndromal categories (cognitively unimpaired, MCI, dementia), and numeric clinical staging (from Stage 1 cognitively normal to Stage 6 severe dementia) for patients in the AD continuum.

D. Comparative Clinical Effectiveness: Supplemental Information

D1. Detailed Methods

Population, Intervention, Comparators, Outcomes, Timing, and Settings Framework (PICOTS)

Population

The population of interest for this review is adults with early AD, i.e., MCI due to AD and mild AD dementia. This population approximates patients whose condition would be categorized as Stages 2 or 3 using diagnostic criteria outlined by the FDA.[66]

We also sought data for subpopulations defined by race/ethnicity, APOE carrier status, and amnestic (vs. non-amnestic) MCI.

Interventions

The intervention of interest for this review is aducanumab in addition to supportive care. Supportive care includes both non-pharmacologic and non-disease-modifying pharmacologic interventions.

Comparators

We compared aducanumab in addition to supportive care to supportive care alone.

Outcomes

The outcomes of interest are described in the list below.

- Patient-important outcomes
    - Ability to maintain independence and autonomy
    - Delayed entry into institutional care
    - Ability to perform activities of daily living (e.g., as measured by AD Cooperative Study-Activities of Daily Living Inventory-MCI)
    - Cognitive function (e.g., as measured by CDR-SB, MMSE)
    - Symptom progression
    - Maintenance of identity and personality
    - Quality of life

    - Emotional wellbeing
    - Behavioral change
    - Ability to communicate
    - Adverse events including:
        - Discontinuation due to adverse events
        - Death
- Other outcomes
    - Caregiver impact
        - Caregiver quality of life
        - Caregiver health
        - Caregiver productivity
    - Level of amyloid beta (e.g., PET)
    - Neuroinflammation
    - ARIA-E and ARIA-H
    - Brain atrophy
    - Level of tau proteins (e.g., CSF phosphorylated tau, PET ligand)

Timing

Evidence on intervention efficacy, safety, and effectiveness were collected from studies of any duration.

Settings

All relevant settings were considered with a particular focus on the outpatient setting.

Table D1. PRISMA 2009 Checklist

		Checklist Items
TITLE		
Title	1	Identify the report as a systematic review, meta-analysis, or both.
ABSTRACT		
Structured Summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.
INTRODUCTION		
Rationale	3	Describe the rationale for the review in the context of what is already known.
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).
METHODS		
Protocol and Registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.
Eligibility Criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.
Information Sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.
Study Selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).
Data Collection Process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.
Data Items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.
Risk of Bias in Individual Studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.
Summary Measures	13	State the principal summary measures (e.g., risk ratio, difference in means).
Synthesis of Results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I2) for each meta-analysis.
Risk of Bias Across Studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).
Additional Analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.

		Checklist Items
RESULTS		
Study Selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.
Study Characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.
Risk of Bias Within Studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).
Results of Individual Studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.
Synthesis of Results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.
Risk of Bias Across Studies	22	Present results of any assessment of risk of bias across studies (see Item 15).
Additional Analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).
DISCUSSION		
Summary of Evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.
FUNDING		
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.

From: Moher D, Liberati A, Tetzlaff J, Altman DG. The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097.

Data Sources and Searches

Procedures for the systematic literature review assessing the evidence on aducanumab for AD followed established best research methods.[67,68] We conducted the review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[69] The PRISMA guidelines include a checklist of 27 items, which are described further in Table D1.

We searched MEDLINE and EMBASE for relevant studies. Each search was limited to English-language studies of human subjects and excluded articles indexed as guidelines, letters, editorials, narrative reviews, case reports, or news items. We included abstracts from conference proceedings identified from the systematic literature search. All search strategies were generated utilizing the Population, Intervention, Comparator, and Study Design elements described above. The proposed search strategies included a combination of indexing terms (MeSH terms in MEDLINE and EMTREE terms in EMBASE), as well as free-text terms.

To supplement the database searches, we performed manual checks of the reference lists of included trials and systematic reviews and invited key stakeholders to share references germane to the scope of this project. We also supplemented our review of published studies with data from conference proceedings, regulatory documents, information submitted by manufacturers, and other grey literature when the evidence met ICER standards (for more information, see https://icer.org/policy-on-inclusion-of-grey-literature-in-evidence-reviews/).

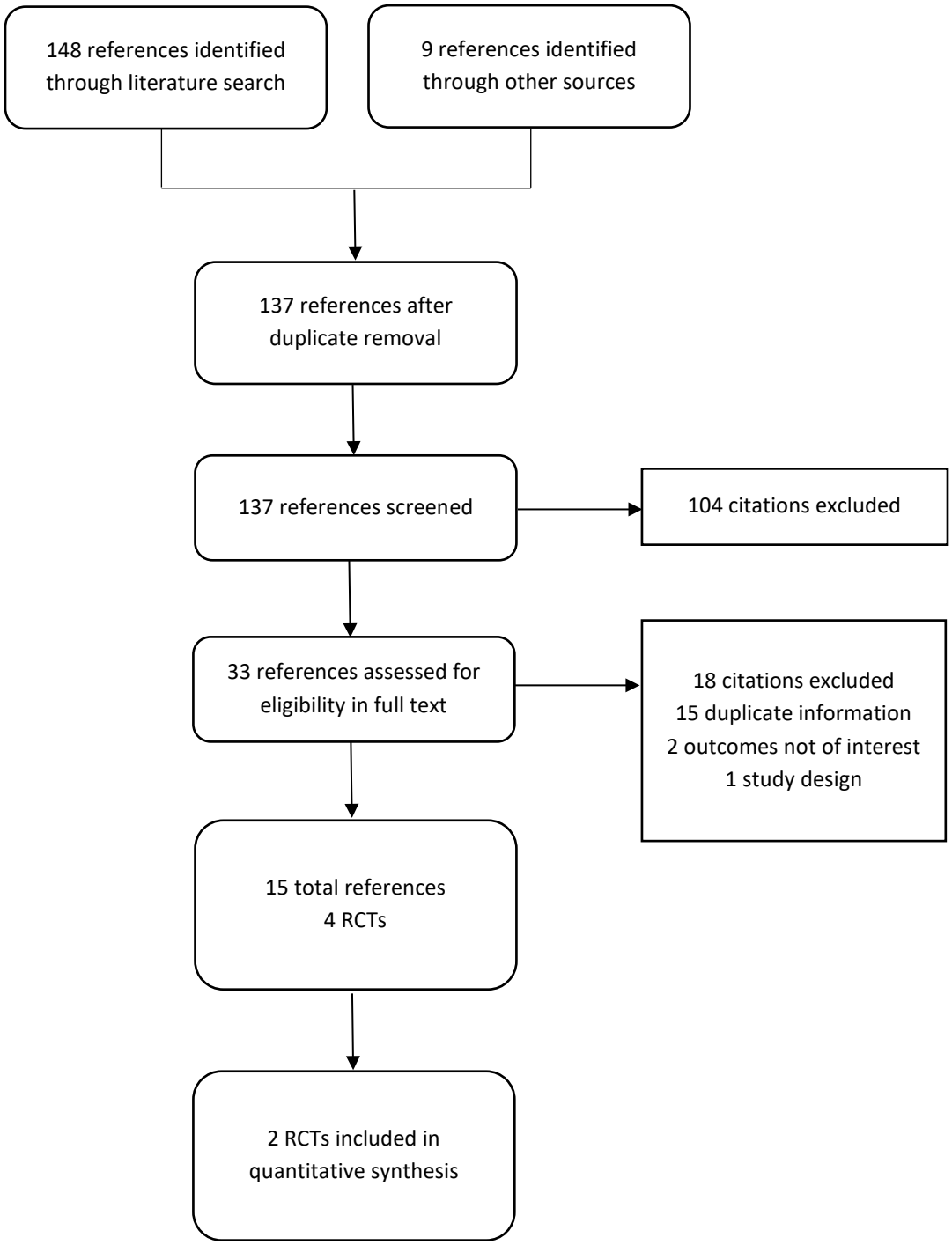
Table D2. Search Strategy of Ovid for Aducanumab MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, Ovid MEDLINE and Versions(R) 1946 to Present

1	(aducanumab or BIIB037 or "BIIB 037" or BIIB-037 or BIIB37 or BIIB-37).ti,ab
2	(addresses or autobiography or bibliography or biography or comment or congresses or consensus development conference or duplicate publication or editorial or guideline or in vitro or interview or lecture or legal cases or legislation or letter or news or newspaper article or patient education handout or periodical index or personal narratives or portraits or practice guideline or review or video audio media).pt.
3	1 NOT 2
4	(exp animals/ or exp animal/ or exp nonhuman/ or exp animal experiment/ or animal model/ or animal tissue/ or non human/ or (rat or rats or mice or mouse or swine or porcine or murine or sheep or lambs or pigs or piglets or rabbit or rabbits or cat or cats or dog or dogs or cattle or bovine or monkey or monkeys or trout or marmoset$1 or basic research or cell lines or in vitro or animal model or canine).tw.) not (humans/ or human/ or human experiment/ or (human* or men or women or patients or subjects).tw.)
5	3 NOT 4
6	limit 5 to English language
7	Remove duplicates from 6
Updated Search on May 18, 2021.	

Table D3. Search Strategy of EMBASE for Aducanumab

#1	'aducanumab/'
#2	aducanumab:ti,ab OR biib037:ti,ab OR 'biib 037':ti,ab OR biib37:ti,ab OR 'biib-37':ti,ab
#3	#1 OR #2
#4	#3 NOT ('case report'/de OR 'human tissue'/de OR 'nonhuman'/de OR 'practice guideline'/de OR 'questionnaire'/de OR 'chapter'/it OR 'conference review'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it OR 'review'/it OR 'short survey'/it)
#5	('animal'/exp OR 'nonhuman'/exp OR 'animal experiment'/exp) NOT 'human'/exp
#6	#4 NOT #5
#7	#6 AND [english]/lim
Updated Search on May 18, 2021.	

Figure D1. PRISMA Flowchart Showing Results of Literature Search for Aducanumab



Study Selection

We performed screening at both the abstract and full-text level. Two investigators independently screened all abstracts identified through electronic searches using DistillerSR (Evidence Partners, Ottawa, Canada) according to the inclusion and exclusion criteria described earlier. We did not exclude any study at abstract-level screening due to insufficient information. We retrieved the citations that were accepted during abstract-level screening for full text appraisal. Two investigators reviewed full papers and provided justification for exclusion of each excluded study.

We also included FDA documents related to aducanumab for AD. These included the manufacturer's submission to the agency, internal FDA review documents, and the transcript of Advisory Committee deliberations and discussions. All literature that did not undergo a formal peer review process is described separately.

Data Extraction and Quality Assessment

Two reviewers extracted key information from the full set of accepted trials. We used criteria published by the US Preventive Services Task Force (USPSTF) to assess the quality of RCTs and comparative cohort studies, using the categories "good," "fair," or "poor."[70] Guidance for quality ratings using these criteria is presented below, as is a description of any modifications we made to these ratings specific to the purposes of this review.

Good*: Meets all criteria: Comparable groups are assembled initially and maintained throughout the study; reliable and valid measurement instruments are used and applied equally to the groups; interventions are spelled out clearly; all important outcomes are considered; and appropriate attention is paid to confounders in analysis. In addition, ITT analysis is used for RCTs.*

Fair*: Studies were graded "fair" if any or all of the following problems occur, without the fatal flaws noted in the "poor" category below: Generally comparable groups are assembled initially but some question remains whether some (although not major) differences occurred with follow-up; measurement instruments are acceptable (although not the best) and generally applied equally; some but not all important outcomes are considered; and some but not all potential confounders are addressed. ITT is done for RCTs.*

Poor*: Studies were graded "poor" if any of the following fatal flaws exists: Groups assembled initially are not close to being comparable or maintained throughout the study; unreliable or invalid measurement instruments are used or not applied equally among groups (including not masking outcome assessment); and key confounders are given little or no attention. For RCTs, ITT analysis is lacking.*

Note that case series are not considered under this rating system – because of the lack of comparator, these are generally considered to be of poor quality.

Assessment of Level of Certainty in Evidence

We used the ICER Evidence Rating Matrix to evaluate the level of certainty in the available evidence of a net health benefit among each of the interventions of focus.[71,72]

Assessment of Bias

As part of our quality assessment, we evaluated the evidence base for the presence of potential publication bias. Given the emerging nature of the evidence base for newer treatments, we performed an assessment of publication bias for aducanumab using clinicaltrials.gov. Search terms included "aducanumab," "BIIB037," and "Alzheimer's disease." We selected studies which would have met our inclusion criteria and for which no findings have been published. We provided qualitative analysis of the objectives and methods of these studies to ascertain whether there may be a biased representation of study results in the published literature.

Data Synthesis and Statistical Analyses

Relevant data on key outcomes of the main studies were summarized qualitatively and quantitatively in the body of the review. Key differences between the studies in terms of the study design, patient characteristics, interventions (including dosing and frequency), outcomes (including definitions and methods of assessments), and study quality were explored in the text of the report. The feasibility of conducting a quantitative synthesis was evaluated by looking at trial populations, design, analytic methods, and outcome assessments across outcomes of interest in the aducanumab trials.

Two Phase III trials (EMERGE and ENGAGE) were included in random effects pairwise meta-analyses of the primary and secondary endpoints (78-week change from baseline in CDR-SB, MMSE, ADAS-COG-13, and ADCS-ADL-MCI). The analyses were conducted in Stata/SE 16.1 using a restricted maximum-likelihood model.

Evidence Base

The Phase Ib (PRIME) trial was a 12-month trial designed to evaluate the safety and tolerability of aducanumab in participants 50-90 years of age with prodromal AD or mild AD dementia.[25] The trial randomized 196 patients to placebo, fixed dosing of 1, 3, 6, or 10 mg/kg, or a titration regimen up to 10 mg/kg; the titration arm comprised only APOE ε4 carriers, while the other arms were stratified by APOE ε4 status. Relative to the Phase III trials, PRIME included participants whose disease was more advanced; patients could participate if they had an MMSE of 20 or higher

(ENGAGE and EMERGE required a minimum score of 24) and a CDR global score of 0.5 or 1 (all participants in ENGAGE and EMERGE had a score of 0.5).

Whereas participants in the high-dose arm of ENGAGE and EMERGE received 14 doses of 10 mg/kg over 78 weeks, the patients in PRIME received 14 doses of 10 mg/kg over 54 weeks.[25] The titration regimen arm of PRIME increased dosing up to 10 mg/kg over 44 weeks (compared to 24 weeks in ENGAGE and EMERGE). The FDA considered the fixed 10 mg/kg arm from PRIME to be the most relevant comparison group to ENGAGE and EMERGE.

Although PRIME was primarily a safety and tolerability study, the CDR-SB and MMSE were included as exploratory clinical endpoints. At week 52, the CDR-SB was 1.26 units lower (i.e., more favorable, 95% CI [-2.36 to -0.16]) in the 10 mg/kg group versus placebo.[25] The change in MMSE was also more favorable in the 10 mg/kg dose group than placebo arm (difference of 1.91 [95% CI 0.06 to 3.75]). The degree to which these results compare to ENGAGE and EMERGE is uncertain, as there was greater decline in the placebo arm of PRIME (1.89 worsening on CDR-SB relative to 1.56 and 1.74 in ENGAGE and EMERGE, respectively). There was a high rate of study withdrawal (34%) and treatment discontinuation (38%) in the trial.

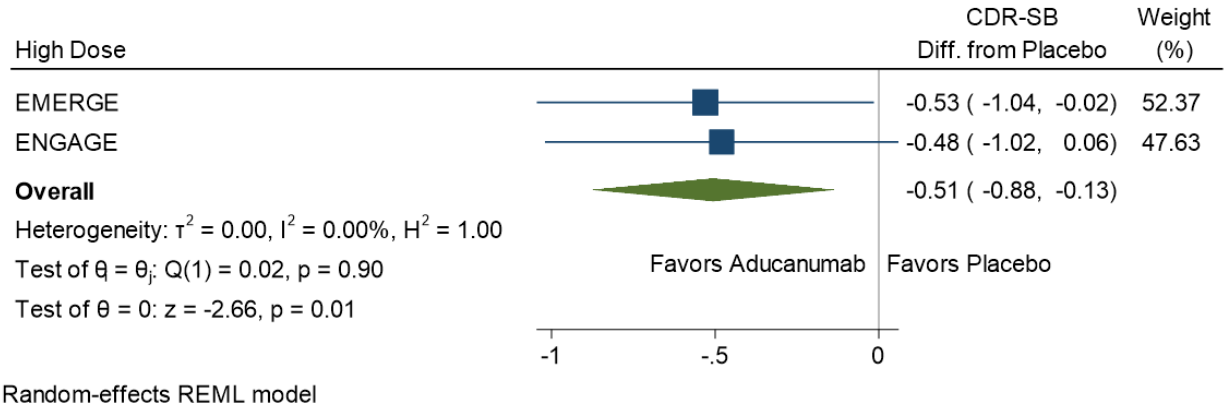
D2. Supplemental Results

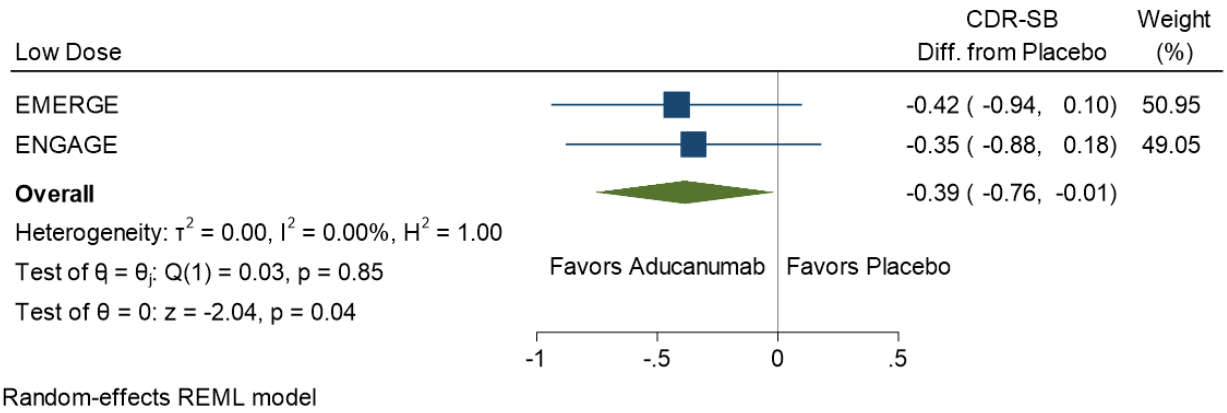
Clinical Benefits

Cognition and Function: CDR-SB

We also conducted a meta-analysis of the change in CDR-SB score from ENGAGE and EMERGE in patients who consented to PV4 prior to week 16 (Figure D2). The pooled high-dose and low-dose treatment effects were statistically significant (high-dose difference in CDR-SB vs. placebo -0.51 [95% CI -0.88 to -0.13]; low-dose difference -0.39 [95% CI -0.76 to -0.01]).

Figure D2. Meta-Analysis of Difference in CDR-SB versus Placebo in Post-PV4 Population





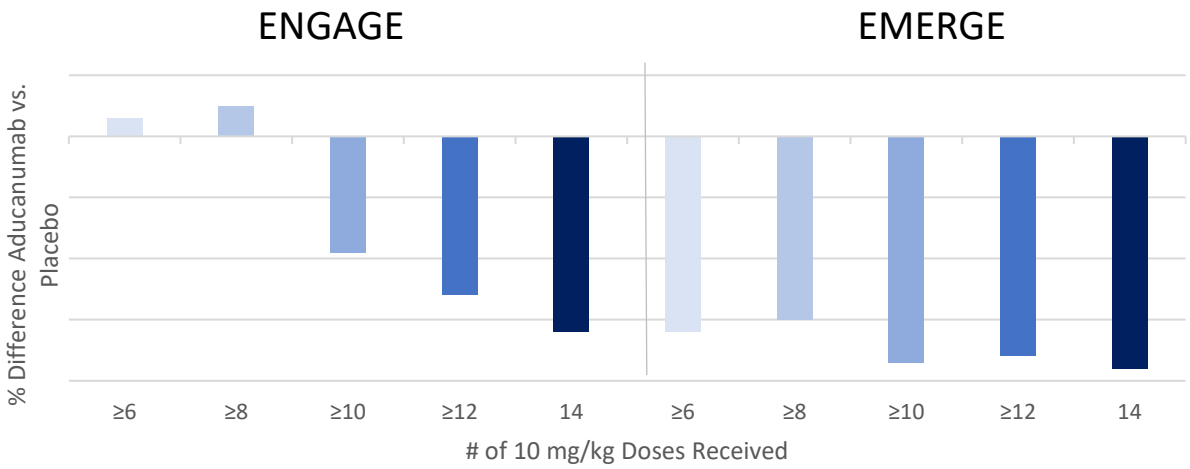
CDR-SB: Clinical Dementia Rating-Sum of Boxes, PV4: Protocol Version 4, REML: restricted maximum likelihood

Post-Hoc Analyses of Post-Randomization Subgroups

Investigators stratified patients by the total cumulative dose received during the trial as well as the number of 10 mg/kg doses they received. In the cumulative dose analysis, patients who received at least 150 mg/kg had a similarly favorable change in CDR-SB score in both trials.[25] Nevertheless, results were divergent among patients who were treated with 100-149 mg/kg (CDR-SB was 20% worse than placebo in ENGAGE, but 33% better than placebo in EMERGE). When stratified by the number of 10 mg/kg doses received, the results in both studies trended positive for patients with at least 10 doses (Figure D3). However in this latter analysis, the worst placebo decline, a 1.58 worsening of CDR-SB, was matched to the highest dose category of 14 doses, and a less severe placebo decline of 1.36 was matched to the ≥8 doses group. This led the FDA's statistical reviewer to express concern that the propensity score matching may have been inadequate.

Another version of this analysis divided patients into categories based on number of 10 mg/kg doses (0-5, 6-12, or ≥13, Figure D4). This analysis suggested that in ENGAGE, it was only the highest category in which the CDR-SB results trended in a favorable direction. Given that these analyses broke randomization, it is uncertain whether the better CDR-SB scores in patients with greater exposure was due to the efficacy of the drug or other unobserved factors.

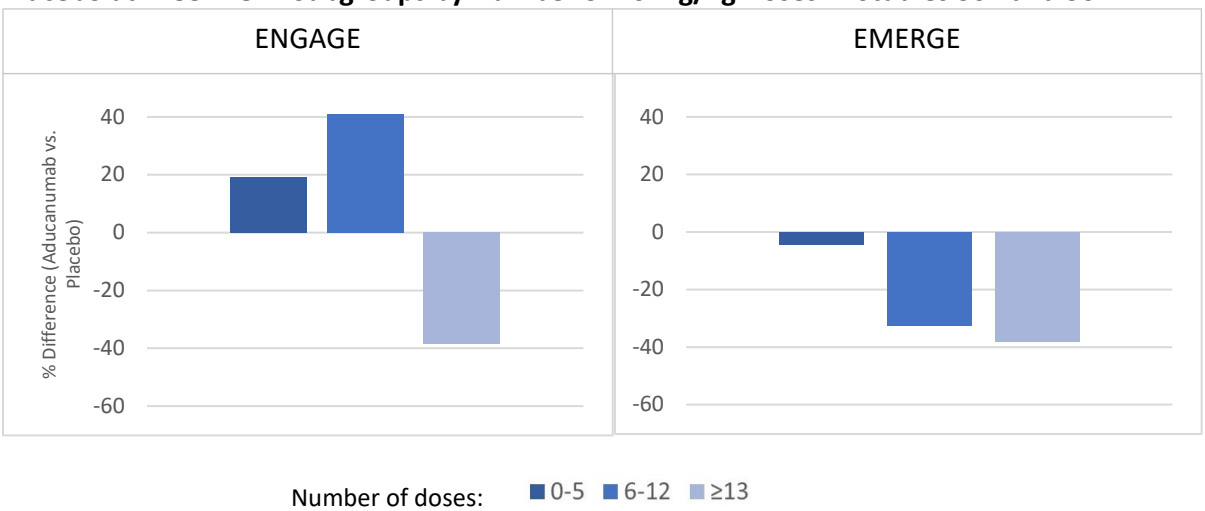
Figure D3. Post-Hoc Analysis of Adjusted Mean Change from Baseline in CDR-SB: % Difference from Propensity-Matched Placebo by Number of 10 mg/kg Doses Received[25]



	ENGAGE					EMERGE				
	≥6	**≥8**	**≥10**	**≥12**	**14**	**≥6**	**≥8**	**≥10**	**≥12**	**14**
Placebo Mean Change from Baseline	1.42 (n=202)	1.36 (n=185)	1.49 (n=157)	1.54 (n=129)	1.58 (n=77)	1.56 (n=220)	1.45 (n=201)	1.54 (n=177)	1.38 (n=144)	1.41 (n=98)
ADU Mean Change from Baseline	1.45 (n=202)	1.43 (n=185)	1.21 (n=157)	1.14 (n=129)	1.08 (n=77)	1.07 (n=220)	1.02 (n=201)	0.97 (n=177)	0.89 (n=144)	0.87 (n=98)

ADU: aducanumab, CDR-SB: Clinical Dementia Rating-Sum of Boxes, mg/kg: milligrams per kilogram, n: number

Figure D4. CDR-SB Adjusted Mean Change from Baseline % Difference from Propensity-Matched Placebo at Week 78 in Subgroups by Number of 10 mg/kg Doses in Studies 301 and 302[25]



Number of Subjects and Adjusted Mean at Week 78

Dose Number	0-5	6-12	≥13	0-5	6-12	≥13
Placebo	131	101	101	106	96	124
	1.31	1.26	1.56	2.03	1.90	1.41
BIIB037	131	101	101	106	96	124
	1.55	1.78	0.97	1.94	1.29	0.87

Source: Figure 49 in ISE.
CDR-SB: Clinical Dementia Rating-Sum of Boxes, mg/kg: milligrams per kilogram
*BIIB037 refers to aducanumab.

Additional Hypotheses to Explain Discordant Results: ARIA

A post-hoc analysis of the CDR-SB that excluded all assessments after the occurrence of ARIA yielded results that were consistent with the primary analysis (Table D4). Similar analyses of the MMSE, which is a performance-based endpoint that may be less susceptible to bias from unblinding than the CDR-SB, also remained consistent.

Table D4. Change from Baseline in CDR-SB at Week 78, With and Without Post-ARIA Observations Excluded[25]

	EMERGE			ENGAGE		
	Placebo Decline	Difference vs. Placebo		Placebo Decline	Difference vs. Placebo	
		Low Dose	High Dose		Low Dose	High Dose
All Observations	1.74	-0.26 (-15%)	-0.39 (-22%)	1.56	-0.18 (-12%)	0.03 (2%)
Excluding Post-ARIA Observations	1.72	-0.19 (-11%)	-0.57 (-33%)	1.55	-0.11 (-7%)	0.00 (0%)

ARIA: amyloid-related imaging abnormalities, CDR-SB: Clinical Dementia Rating-Sum of Boxes

Other Measures of Cognitive Performance, Function, and Behavior

Secondary endpoints in EMERGE and ENGAGE evaluated cognitive performance using the MMSE and ADAS-Cog 13; participants' ability to perform activities of daily activity was assessed with the ADSC-ADL-MCI. The NPI-10, a questionnaire designed to examine behavioral function, was also implemented as a tertiary endpoint.

Results from the MMSE, ADAS-Cog 13, ADCS-ADL-MCI, and NPI-10 were directionally consistent with the primary endpoint results of each respective trial at week 78; nominally statistically significant differences from placebo were observed for the high-dose aducanumab arm for all secondary endpoints of EMERGE, and for no secondary endpoints of ENGAGE (Table D5).[25] Statistical differences were not observed for the low-dose arm of either trial.

Table D5. Secondary Endpoint Analyses from ENGAGE and EMERGE at Week 78

	ENGAGE[25,27]			EMERGE[25,27]		
	Placebo Decline	Difference vs. Placebo (p-value)		Placebo Decline	Difference vs. Placebo (p-value)	
		Low Dose	High Dose		Low Dose	High Dose
MMSE*	-3.5	0.2 (0.48)	-0.1 (0.81)	-3.3	-0.1 (0.76)	0.6 (0.05)
ADAS-Cog 13†	5.14	-0.58 (0.25)	-0.59 (0.26)	5.16	-0.7 (0.20)	-1.4 (0.01)
ADCS-ADL-MCI‡	-3.8	0.7 (0.12)	0.7 (0.15)	-4.3	0.7 (0.15)	1.7 (0.0006)
NPI-10§	1.2	-1.0 (0.05)	0.1 (0.91)	1.5	-0.5 (0.39)	-1.3 (0.02)

ADAS-Cog 13: Alzheimer's Disease Assessment Scale-Cognitive Subscale, ADCS-ADL-MCI: Alzheimer's Disease Cooperative Study Scale for Activities of Daily Living in Mild Cognitive Impairment, MMSE: Mini-Mental State Exam, NPI-10: Neuropsychiatric Inventory 10

*MMSE scores range from 0 to 30, with higher scores indicating less cognitive impairment.

†ADAS-Cog 13 scores range from 0 to 85, with higher scores indicating more cognitive impairment.

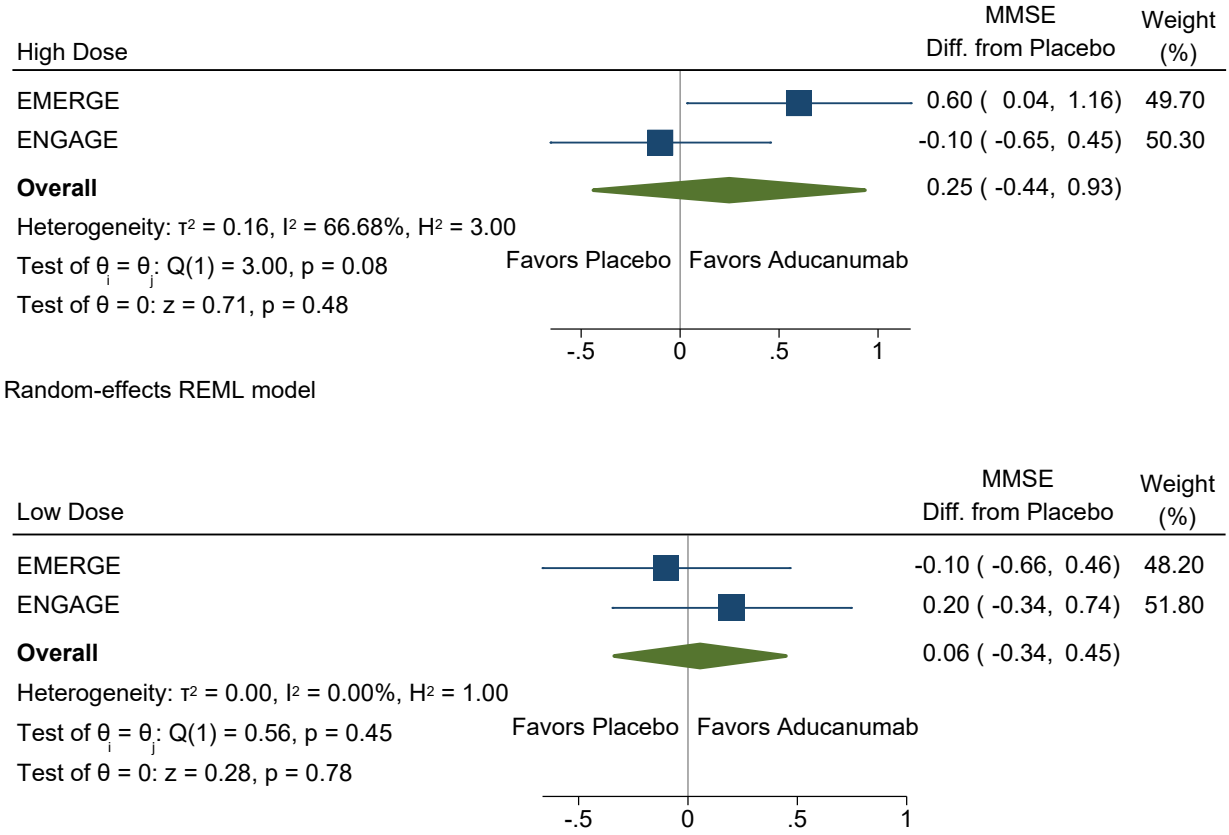
‡ADCS-ADL-MCI scores range from 0 to 53, with higher scores indicating less deterioration.

§NPI-10 scores ranges from 0 to 120, with higher scores indicating worse symptoms.

We conducted additional meta-analyses of the MMSE, ADAS-Cog 13, and ADCS-ADL-MCI. A modestly favorable, statistically-significant effect was observed for high-dose aducanumab in

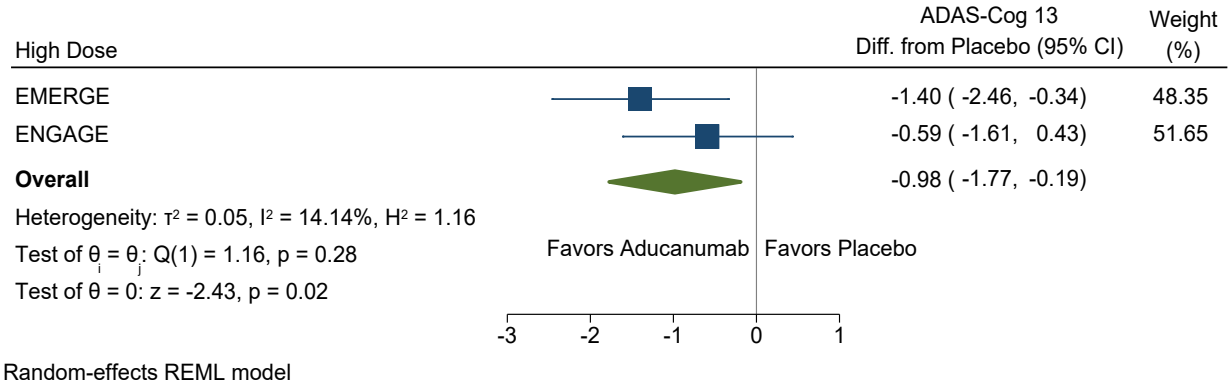
pooled analyses of the ADAS-Cog and ADCS-ADL-MCI as well as the low-dose ADCS-ADL-MCI analysis.

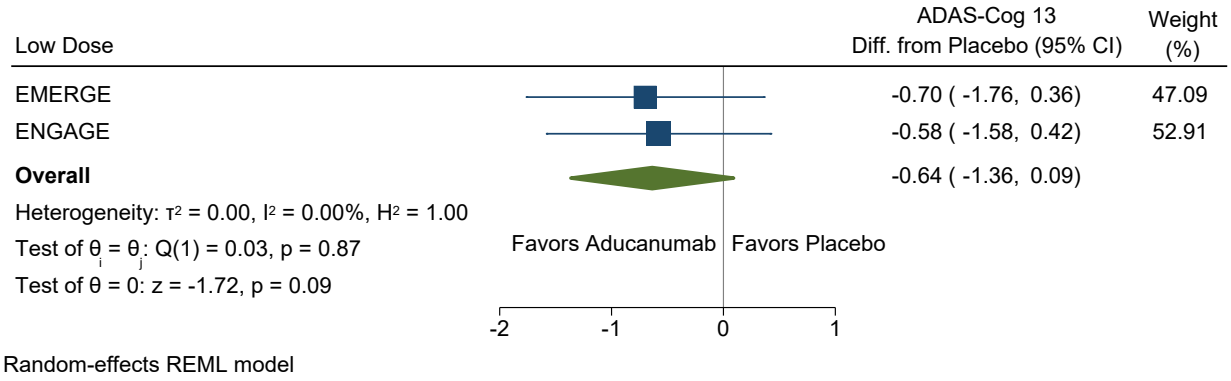
Figure D5. Meta-Analysis of Difference in MMSE at Week 78



MMSE: Mini-Mental State Examination, REML: restricted maximum likelihood
The minimal clinically important difference in AD is estimated to be 1-3 points.

Figure D6. Meta-Analysis of Difference in ADAS – COG (13-Item Version) at Week 78

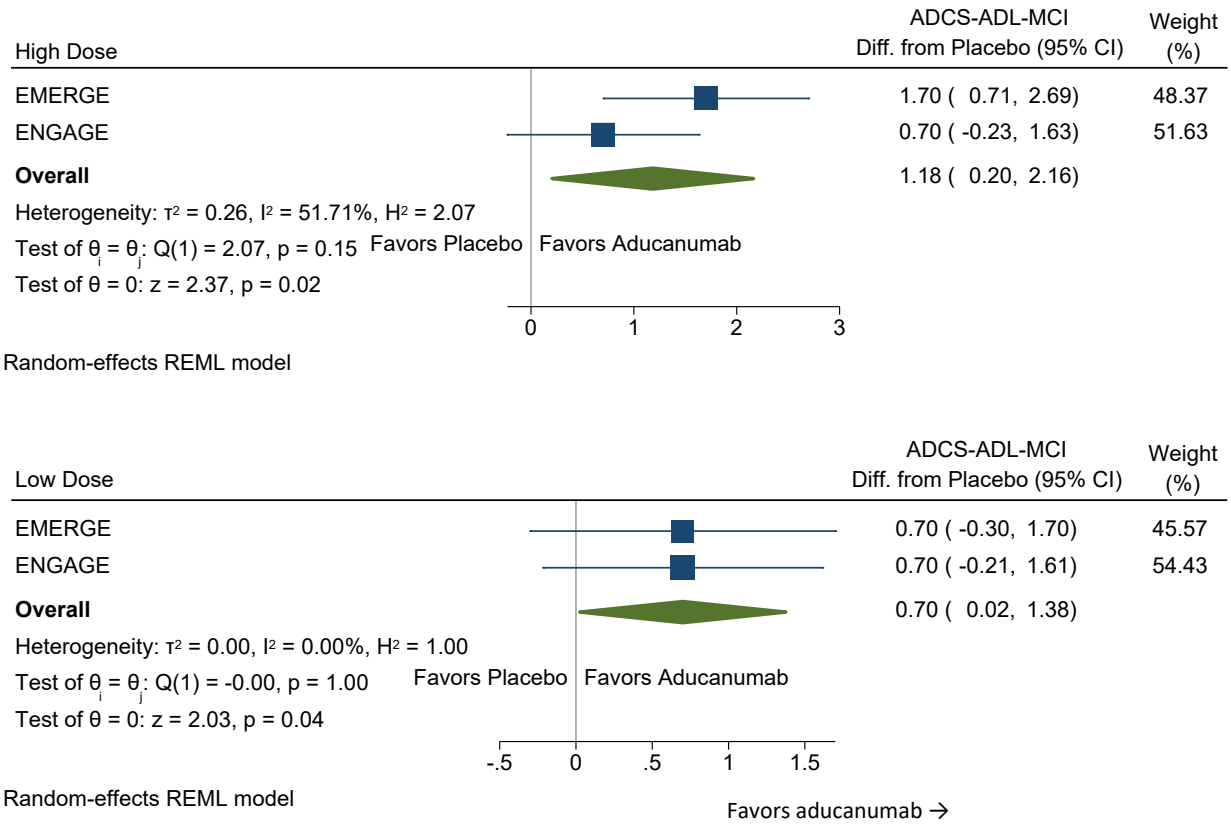




ADAS-Cog 13: Alzheimer's Disease Assessment Scale-Cognitive Subscale (13-Item Version), CI: confidence interval, REML: restricted maximum likelihood

The minimal clinically important difference in early-stage AD is estimated to be 1 to 2 points.

Figure D7. Meta-Analysis of Difference in ADCS – ADL (MCI Version) at Week 78



ADCS-ADL-MCI: Alzheimer's Disease Cooperative Study-Activities of Daily Living-Mild Cognitive Impairment Version, CI: confidence interval, REML: restricted maximum likelihood

Changes in AD-Related Biomarkers

Change from baseline in markers of downstream AD tau pathophysiology and neurodegeneration also suggest a dose-dependent trend in the small subsets of patients (n=53 in ENGAGE, n=78 in EMERGE) in whom these were measured. Results were consistent across studies, with slightly smaller decreases in tau in the ENGAGE trial. Measures of brain atrophy, including volume of the whole brain, whole cortex, and hippocampus were not statistically different between treatment groups at week 78 of either trial.

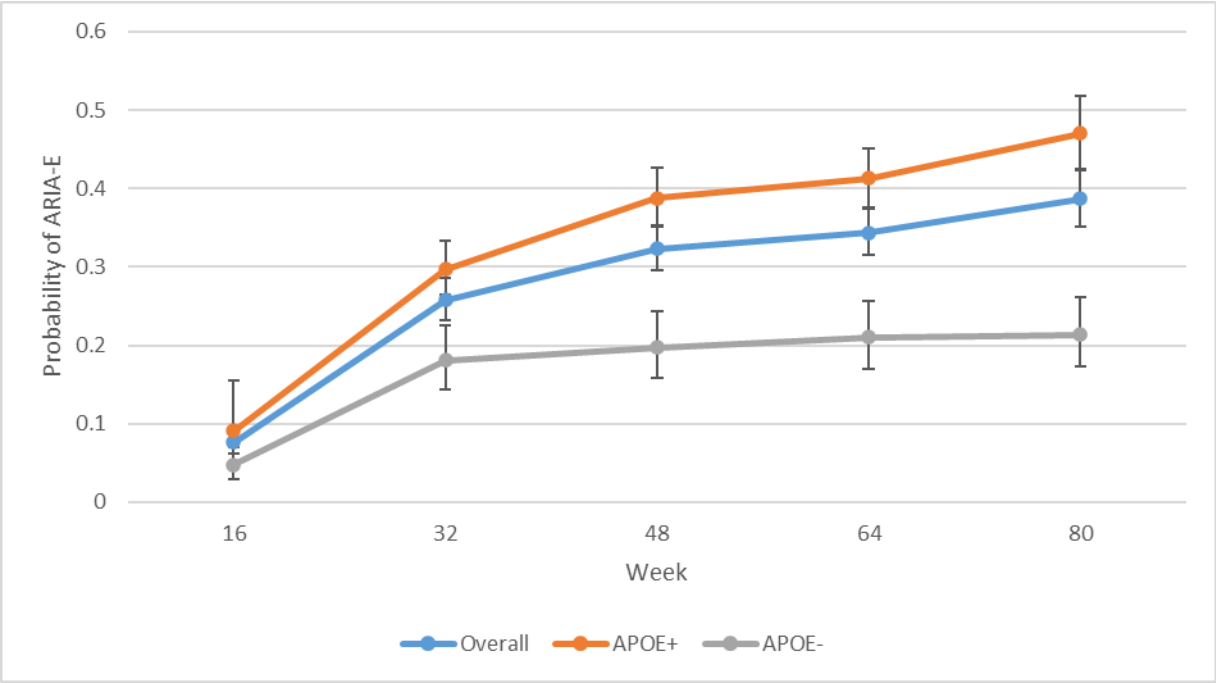
Harms

Table D6. Kaplan-Meier Estimates of Time to First ARIA-E Event by APOE Status[25]

		Population		
		10 mg/kg Overall	10 mg/kg APOE4-	10 mg/kg APOE4+
Estimated Proportion with ARIA-E	**Week 16**			
	# at Risk	938	329	609
	Proportion	0.076 (0.062, 0.094)	0.048 (0.030, 0.077)	0.091 (0.071, 0.155)
	Week 32			
	# at Risk	738	274	464
	Proportion	0.258 (0.232, 0.286)	0.181 (0.144, 0.226)	0.297 (0.264, 0.333)
	Week 48			
	# at Risk	643	255	388
	Proportion	0.323 (0.295, 0.353)	0.197 (0.158, 0.243)	0.388 (0.352, 0.426)
	Week 64			
	# at Risk	536	210	326
	Proportion	0.344 (0.316, 0.375)	0.210 (0.170, 0.257)	0.413 (0.376, 0.451)
	Week 80			
	# at Risk	94	34	60
	Proportion	0.387 (0.351, 0.424)	0.214 (0.173, 0.262)	0.470 (0.425, 0.518)

APOE4: apolipoprotein E, ARIA: amyloid-related imaging abnormality, mg/kg: milligrams per kilogram

Figure D8. Kaplan-Meier Estimates of Time to First ARIA-E Event by APOE Status[25]



APOE: apolipoprotein, ARIA: amyloid-related imaging abnormality

D3. Methodologic Considerations

Many of the controversies involved in interpreting the results of ENGAGE and EMERGE involve issues rooted in clinical epidemiology and biostatistics. We reflect on some of these issues here and our interpretations of their importance.

- ENGAGE and EMERGE were stopped early for futility. After that decision, questions were raised about whether the futility rule was correctly applied and whether it was appropriate to analyze these trials for benefit once this had occurred. Overall, we do not have significant concerns about analyzing the results from these trials despite the prior futility assessment. Stopping a trial for futility can be associated with underestimating a treatment effect.[73]
- At the FDA Advisory Committee Meeting, the FDA and the manufacturer suggested that the Phase Ib PRIME trial provided a second positive trial of aducanumab, making the ENGAGE trial the outlier as it was the only negative trial among three trials. Members of the Advisory Committee raised concerns that, since ENGAGE and EMERGE would never have been performed had PRIME been negative, that the results from PRIME do not provide important supporting evidence for the efficacy of aducanumab. We believe this overly discounts the results of PRIME. If Phase III trials are only performed after a positive earlier trial that "gates" the performance of those trials, then the prior likelihood of a drug working when Phase III trials are performed is clearly increased by this gating; not all drugs make it to Phase III and the initial "gating" trials should not all be assumed to be positive due to chance. However, that does not mean that PRIME should be considered as providing equivalent confirmatory evidence as would have been achieved had ENGAGE been positive. Any boost in prior probability of efficacy from PRIME must also be weighed against the difficult-to-estimate negative priors related to the many clinical failures of anti-amyloid therapies. Furthermore, PRIME was a small study with differential loss to follow-up in the high-dose aducanumab and placebo groups.
- Given concerns that baseline risk for being a "rapid progressor" was unbalanced between the trial arms in ENGAGE, analyses were presented that excluded these patients. In the absence of any prior plan to analyze the data in this way, and without a prior definition of a rapid progressor, this sort of post-hoc analysis is highly risky and breaks randomization in serious ways. Randomization is intended to balance baseline risks and while this is not guaranteed by randomization, excluding patients based on outcomes is generally not helpful in understanding the results of a randomized trial. As an example, one could imagine that aducanumab actually increases the risk for rapid progression, and so the results of ENGAGE accurately capture that risk. If this were the case, excluding these patients would miss a major harm of aducanumab.
- Concerns were raised by the Advisory Committee and FDA statistician that "functional unblinding" due to ARIA could explain the discordant results. The hypothesis is that with

exposure of APOE ε4 patients to higher doses of aducanumab, more asymptomatic ARIA occurred, and this led to dosing interruptions and repeated MRI scans alerting patients and caregivers to which trial arm they were in. Since CDR-SB is based on patient and caregiver report, knowledge that patients were on active therapy could bias those unblinded reporters. We think this is a relatively unlikely explanation for the results both because many patients in ENGAGE would also have experienced functional unblinding and because the MMSE results in both EMERGE and ENGAGE track with the CDR-SB results, yet should be less susceptible to functional unblinding. MMSE is an objective measure. That said, we believe that future studies should protect against functional unblinding due to ARIA. It would be appropriate to have protocols in which ARIA is reported to clinicians, investigators, patients, and families for those in the placebo arms of trials at the same rate as is seen in the active arms. Placebo could be held and MRIs performed at the same rates so as to maintain blinding. This has been used previously for trials where one therapy requires adjustment based on a laboratory test such as drug levels or clotting parameters. Similar "adjustment" in patients not receiving that drug maintains blinding.

- Most concerningly, the manufacturer appears to have analyzed the data starting from the assumption that the discordant results were due to benefit having been missed in ENGAGE. Although an analysis looking at PV4 patients with the opportunity to complete provides an analysis in which the data from ENGAGE for patients who received high-dose aducanumab appear to be concordant with EMERGE, this is likely one of many exploratory analyses performed to understand why ENGAGE was not a positive trial. As such, issues of multiple testing become extremely problematic. This is why it is imperative to analyze studies according to pre-planned protocols. Even with this particular analysis of ENGAGE, a consistent story across high and low doses of ENGAGE and EMERGE is not seen. We are very concerned that this post-hoc explanation for the discordant results may be more likely to reflect the play of chance and a selection of analyses that overly focus on confirming the positive results in EMERGE.

D4. Evidence Tables

Table D7. Study Design

Author & Year of Publication (Trial)	Study Design & Duration of Follow-Up	Population, N	Interventions & Dosing Schedule	Inclusion and Exclusion Criteria
EMERGE (302)[25] NCT02484547 ENGAGE (301)[25] NCT02477800	Two Phase III Global, Double-Blind, Placebo-Controlled, RCTs 18-month DB PC treatment period followed by dose-blinded LTE Randomization stratified by APOE ε4 status	Patients with early AD (MCI due to AD or mild AD dementia) **Study 302:** N=1638 **Study 301:** N=1647 **Overall:** N=3285	1. Low-dose aducanumab 2. High-dose aducanumab 3. Placebo IV infusion every 4 weeks Dosing Protocol V. 1-3 • Low-dose APOE ε4 Carriers: 3 mg/kg after titration over 8 weeks • Low-dose APOE ε4 Non-Carriers: 6 mg/kg after titration over 24 weeks • High-dose APOE ε4 Carrier: 6 mg/kg after titration over 24 weeks • High-dose APOE ε4 Non-Carriers: 10 mg/kg after titration over 24 weeks Dosing Protocol V. 4-6 • Low dose: Unchanged • High dose: 10 mg/kg (after titration over 24 weeks) in all participants regardless of participants APOE ε4 status	**Key Inclusion** • Must meet all following clinical criteria for MCI due to AD or mild AD: • CDR-Global Score of 0.5 • Objective evidence of cognitive impairment at screening • An MMSE score between 24 and 30 (inclusive) • Must have a positive amyloid PET • Must consent to APOE genotyping • If using drugs to treat symptoms related to AD, doses must be stable for at least 8 weeks prior to screening visit 1 **Key Exclusion** • Any uncontrolled medical or neurological condition (other than AD) that may be a contributing cause of the subject's cognitive impairment • Clinically significant unstable psychiatric illness within 6 months prior to screening • Transient ischemic attack or stroke or any unexplained loss of consciousness within 1 year prior to screening • Brain MRI performed at screening that shows evidence of any of following: acute or sub-acute hemorrhage, prior microhemorrhage or prior subarachnoid hemorrhage (unless finding is not due to an underlying structural or vascular hemorrhage), ≥4 microhemorrhages, cortical infarct, >1 lacunar infarct, superficial siderosis or history of diffuse white matter disease • Contraindications to having a brain MRI or PET scan • History of bleeding disorder • Use of medications with platelet anti-aggregant or anti-coagulant properties (unless aspirin at ≤325 mg daily)

Author & Year of Publication (Trial)	Study Design & Duration of Follow-Up	Population, N	Interventions & Dosing Schedule	Inclusion and Exclusion Criteria
				• Participation in any active immunotherapy study targeting Aβ, any passive immunotherapy study targeting Aβ within 12 months of screening or any study with purported disease-modifying effect in AD within 12 months of screening unless documentation of receipt of placebo
Phase IB (PRIME 103)[25] NCT01677572	Phase Ib, DB, PC, Multiple Dose Study 12-month treatment period with dose escalation and staggered cohorts with dose-blinded aducanumab LTE period	Prodromal AD and mild AD dementia N=197	**12-month PC period:** ADU (1, 3, 6, 10 mg/kg in a fixed dose regiment or 10 mg/kg after 44-week titration) or PBO in a 3:1 or 3:2 ratio 1. Placebo (n=48) 2. 1 mg/kg (n=31) 3. mg/kg (n=32) 4. 6 mg/kg (n=30) 5. 10 mg.kg (n=32) 6. Titration APOE E4 carriers 1 to 10 mg/kg (n=23) Randomization: 3:1 active:placebo; fixed-dose within cohorts stratified by APOE E4 status with 14 total doses in each arm 36-month LTE period: dose-blinded ADU	**Key Inclusion** *Prodromal AD* • MMSE score between 24-30 • Spontaneous memory complaint • Objective memory loss defined as free recall score of <27 on the FCSRT • Global CDR score of 0.5 *Mild AD* • MMSE score between 20-26 • Global CDR score of 0.5 or 1.0 • Meeting National Institute on Aging-Alzheimer's Association core clinical criteria for probable AD • Positive PET • Consent to APOE genotyping **Key Exclusion** • Medical or neurological condition (other than AD) that may be contributing to cognitive impairment • Stroke or TIA or unexplained loss of consciousness in past year • Clinically significant psychiatric illness in past 6 months • History of unstable angina, MI, chronic heart failure, or clinically significant conduction abnormalities within 1 year prior to screening • Contraindications to PET • Negative PET with any amyloid targeting ligand within 48 weeks of screening
Phase I (101)[74] NCT01397539	Phase I double-blind, placebo-controlled,	Mild-to-moderate AD N=53	1. Single dose of aducanumab IV in cohorts assigned to an	**Key Inclusion** • Clinical diagnosis of AD • MMSE score of 14 to 26 inclusive

Author & Year of Publication (Trial)	Study Design & Duration of Follow-Up	Population, N	Interventions & Dosing Schedule	Inclusion and Exclusion Criteria
Ferrero 2016	single ascending dose RCT Single Dose with 8 follow-up visits up to 24 weeks after dosing		ascending dose: 0.03, 1, 3, 10, 20, 30, and 60 mg/kg 2. Matched placebo	**Key Exclusion** • Medical or neurological condition other than AD that could be contributing cause of dementia • Clinically significant psychiatric illness within past 6 months • Blood donation within 1 month prior to screening • Participation in other drug, biologic, device, or clinical study or treatment with any investigational drug within 30 days • Contraindications to brain MRI

Aβ: amyloid beta, AD: Alzheimer's Disease, ADU: aducanumab, APOE ε4: apolipoprotein E ε4, CDR: Clinical Dementia Rating scale, DB: double-blind, FCSRT: Free and Cued Selective Reminding Test, IV: intravenous, LTE: long-term extension, MCI: mild cognitive impairment, mg/kg: milligram per kilogram, MI: myocardial infarction, MMSE: Mini-Mental State Examination, MRI: magnetic resonance imaging, N: total number, PC: placebo-controlled, PET: positron emission tomography, RCT: randomized controlled trial, TIA: transient ischemic attack

Table D8. Baseline Characteristics for Phase III Trials: EMERGE and ENGAGE

		EMERGE (302)[75,25]				ENGAGE (301)[75,25]			
Study Arms		**Placebo**	**Low Dose**	**High Dose**	**Overall**	**Placebo**	**Low Dose**	**High Dose**	**Overall**
N		**548**	**543**	**547**	**1638**	**545**	**547**	**555**	**1647**
Age, Mean (SD)		70.8 (7.40)	70.6 (7.45)	70.6 (7.47)	70.7 (7.43)	69.8 (7.72)	70.4 (6.96)	70.0 (7.65)	70.1 (7.45)
Female, n (%)		290 (52.9)	269 (49.5)	284 (51.9)	843 (51.5)	287 (52.7)	284 (51.9)	292 (52.6)	863 (52.4)
Race, n (%)	**Asian**	47 (8.6)	39 (7.2)	42 (7.7)	128 (7.8)	55 (10.1)	55 (10.1)	65 (11.7)	175 (10.6)
	White	431 (78.6)	432 (79.6)	422 (77.1)	1285 (78.4)	413 (75.8)	412 (75.3)	413 (74.4)	1238 (75.2)
Education Years, Mean (SD)		14.5 (3.68)	14.5 (3.63)	14.5 (3.60)	14.5 (3.63)	14.7 (3.66)	14.6 (3.77)	14.6 (3.72)	14.6 (3.71)
AD Medications Used, n (%)		282 (51.5)	281 (51.7)	285 (52.1)	848 (51.8)	299 (54.9)	317 (58.0)	313 (56.4)	929 (56.4)
Concomitant AD Medication, n (%)	**Any AD Medication at Baseline**	282 (51.5)	281 (51.7)	285 (52.1)	848 (51.8)	299 (54.9)	317 (58.0)	313 (56.4)	929 (56.4)
	Cholinesterase Inhibitors	235 (42.9)	230 (42.4)	228 (41.7)	693 (42.3)	242 (44.4)	257 (47.0)	264 (47.6)	763 (46.3)
	Memantine	8 (1.5)	15 (2.8)	21 (3.8)	44 (2.7)	16 (2.9)	15 (2.7)	13 (2.3)	44 (2.7)
	Both Cholinesterase Inhibitors and Memantine	39 (7.1)	36 (6.6)	36 (6.6)	111 (6.8)	41 (7.5)	45 (8.2)	36 (6.5)	122 (7.4)
APOE ε4 Status, n (%)	**Carrier**	368 (67.2)	362 (66.7)	365 (66.7)	1095 (66.8)	376 (69.0)	391 (71.5)	378 (68.1)	1145 (69.5)
	Non-Carrier	178 (32.5)	178 (32.8)	181 (33.1)	537 (32.8)	167 (30.6)	156 (28.5)	176 (31.7)	499 (30.3)
Clinical Stage, n (%)	**MCI due to AD**	446 (81.4)	452 (83.2)	438 (80.1)	1336 (81.6)	443 (81.3)	440 (80.4)	442 (79.6)	1325 (80.4)
	Mild AD	102 (18.6)	91 (16.8)	109 (19.9)	302 (18.4)	102 (18.7)	107 (19.6)	113 (20.4)	322 (19.6)
Amyloid PET SUVR, Mean Composite (SD), n *(Sub-Study – Not Full Population)*		1.38 (0.17), 159	1.40 (0.18), 159	1.38 (0.18), 170	1.38 (0.18), 488	1.38 (0.20), 204	1.39 (0.19), 198	1.41 (0.18), 183	1.39 (0.19), 585
RBANS Delayed Memory Score, Mean (SD)		60.5 (14.23)	60.0 (14.02)	60.7 (14.15)	NR	60.0 (13.65)	59.5 (14.16)	60.6 (14.09)	NR
MMSE Score, Mean (SD)		26.4 (1.78)	26.3 (1.72)	26.3 (1.68)	26.3 (1.73)	26.4 (1.73)	26.4 (1.78)	26.4 (1.77)	26.4 (1.76)
CDR Global Score	**0.5**	544 (99.3)	543 (100)	546 (99.8)	NR	544 (99.8)	546 (99.8)	554 (99.8)	NR
	1	3 (0.5)	0 (0)	1 (0.2)	NR	1 (0.2)	1 (0.2)	0 (0)	NR
CDR-SB Score, Mean (SD)		2.47 (1.00)	2.46 (1.01)	2.51 (1.05)	2.48 (1.02)	2.40 (1.01)	2.43 (1.01)	2.40 (1.01)	2.41 (1.01)
ADAS-Cog 13 Score, Mean (SD)		21.9 (6.7)	22.5 (6.8)	22.2 (7.1)	22.2 (6.9)	22.5 (6.6)	22.5 (6.3)	22.4 (6.5)	22.5 (6.5)
ADCS-ADL-MCI Score, Mean (SD)		42.6 (5.7)	42.8 (5.5)	42.5 (5.2)	42.6 (5.7)	43.0 (5.6)	42.9 (5.7)	42.9 (5.7)	42.9 (5.7)

AD: Alzheimer's disease, ADAS-Cog 13: Alzheimer's Disease Assessment Scale-Cognitive 13-Item Scale, ADCS-ADL-MCI: Alzheimer's Disease Cooperative Study-Activities of Daily Living-Mild Cognitive Impairment, APOE ε4: apolipoprotein Eε4, CDR: Clinical Dementia Rating scale, CDR-SB: Clinical Dementia Rating Scale-Sum of Boxes, MCI: mild cognitive impairment, mg/kg: milligram per kilogram, MMSE: Mini-Mental State Examination, n: number, N: total number, NR: not reported, PET: positron emission tomography, RBANS: Repeatable Battery for the Assessment of Neuropsychological Status, SD: standard deviation, SUVR: standard uptake value ratio

Table D9. Baseline Characteristics for Phase I Trials

		Phase IB (PRIME 103)[25,76]			Phase I (101)[74]	
Study Arms		**Placebo**	**10 mg/kg**	**Overall**	**Placebo**	**10 mg/kg**
N		**48**	**32**	**196**	**14**	**6**
Age, Mean (SD)		73.3 (6.82)	73.7 (8.33)	72.8 (7.93)	66.9 (8.7)	72.7 (4.5)
Female, n (%)		28 (58)	15 (47)	98 (50)	9 (64)	5 (83)
Race, n (%)	**Asian**	0 (0)	1 (3)	1 (<1)	0 (0)	1 (17)
	White	48 (100)	30 (94)	191 (97)	13 (93)	5 (83)
Education Years, Mean (SD)		15.5 (2.98)	15.2 (2.35)	15.4 (2.84)	NR	NR
AD Medications Used, n (%)		32 (67)	15.2 (2.35)	15.4 (2.84)	NR	NR
Concomitant AD Medication, n (%)	**Any AD Medication at Baseline**	32 (67)	17 (53)	130 (66)	NR	NR
	Cholinesterase Inhibitors	30 (63)	17 (53)	124 (63)	NR	NR
	Memantine	12 (25)	5 (16)	39 (20)	NR	NR
	Both Cholinesterase Inhibitors and Memantine	NR	NR	NR	NR	NR
APOE ε4 Status, n (%)	**Carrier**	34 (71)	20 (63)	138 (70)	4 (29)	4 (67)
	Non-Carrier	14 (29)	12 (38)	58 (30)	10 (71)	2 (33)
Clinical Stage, n (%)	**Prodromal AD**	22 (46)	13 (41)	84 (43)	NR	NR
	Mild AD	26 (54)	19 (59)	112 (57)	NR	NR
Amyloid PET SUVR, Mean Composite (SD), n		1.39 (0.19), 585	1.44 (0.17), 48	1.44 (0.19), 32	NR	NR
RBANS Delayed Memory Score, Mean (SD)		NR	NR	NR	NR	NR
MMSE Score, Mean (SD)		24.7 (3.6)	24.8 (3.1)	NR	22.1 (2.4)	18.3 (4.9)
CDR Global Score	**0.5**	40 (83)	24 (75)	151 (77)	NR	NR
	1	8 (17)	8 (25)	45 (23)	NR	NR
CDR-SB Score, Mean (SD)		2.69 (1.54)	3.14 (1.71)	3.17 (1.74)	NR	NR
ADAS-Cog 13 Score, Mean (SD)		NR	NR	NR	17.0 (6.5)	32.8 (20.8)
ADCS-ADL-MCI Score, Mean (SD)		NR	NR	NR	NR	NR

AD: Alzheimer's disease, ADAS-Cog 13: Alzheimer's Disease Assessment Scale-Cognitive 13-Item Scale, ADCS-ADL-MCI: Alzheimer's Disease Cooperative Study-Activities of Daily Living-Mild Cognitive Impairment, APOE ε4: apolipoprotein E ε4, CDR: Clinical Dementia Rating scale, CDR-SB: Clinical Dementia Rating Scale-Sum of Boxes, mg/kg: milligram per kilogram, MMSE: Mini-Mental State Examination, n: number, N: total number, NR: not reported, PET: positron emission tomography, RBANS: Repeatable Battery for the Assessment of Neuropsychological Status, SD: standard deviation, SUVR: standard uptake value ratio

Table D10. Efficacy Outcomes I: Key Trials

Trial		EMERGE (302)[25]			ENGAGE (301)[25]			Phase IB (PRIME 103)[25]	
ITT Population									
Study Arms		**Placebo**	**Low Dose**	**High Dose**	**Placebo**	**Low Dose**	**High Dose**	**Placebo**	**High Dose**
Baseline N*		**548**	**543**	**547**	**545**	**547**	**555**	**48**	**32**
Timepoint		**78 Weeks**			**78 Weeks**			**52 Weeks**	
Difference vs. Placebo (%), p-value	**CDR-SB**	PBO decline: 1.74	-0.26 (-15), 0.09	-0.39 (-22), 0.01	PBO decline: 1.56	-0.18 (-12), 0.23	0.03 (2), 0.83	PBO decline: 1.89	-1.26 (-67), 0.02
	MMSE	PBO decline: -3.3	-0.1 (3.0), 0.76	0.6 (-18), 0.05	PBO decline: -3.5	0.2 (-6), 0.48	-0.1 (3), 0.81	PBO decline: -2.45	1.91 (-76), 0.04
	ADAS-Cog 13	PBO decline: 5.16	-0.7 (-14), 0.20	-1.4 (-27), 0.01	PBO decline: 5.14	-0.58 (-11), 0.25	-0.59 (-11), 0.26	NR	NR
	ADCS-ADL-MCI	PBO decline: -4.3	0.7 (-16), 0.15	1.7 (-40), 0.0006	PBO decline: -3.8	0.7 (-18), 0.12	0.7 (-18), 0.15	NR	NR
	NPI-10	PBO decline: 1.5	-0.5 (-33), 0.39	-1.3 (-87), 0.02	PBO decline: 1.2	-1.0 (-83), 0.05	0.1 (8), 0.91	NR	NR
	Amyloid PET SUVR†	PBO decline: 0.014	-0.18 (NR), <0.0001	-0.28 (NR), <0.0001	PBO decline: -0.003	-0.17 (NR), <0.0001	-0.23 (NR), <0.0001	PBO decline: 0.017	-0.28 (-61.1), <0.001

ADAS-Cog 13: Alzheimer's Disease Assessment Scale-Cognitive 13-Item Scale, ADCS-ADL-MCI: Alzheimer's Disease Cooperative Study-Activities of Daily Living – Mild Cognitive Impairment, CDR-SB: Clinical Dementia Rating Scale-Sum of Boxes, ITT: intention-to-treat, mg/kg: milligram per kilogram, MMSE: Mini-Mental State Examination, N: total number, NPI-10: Neuropsychiatric Inventory-10, NR: not reported, PBO: placebo, PET: positron emission tomography, SUVR: standard uptake value ratio

*Baseline N is reported. Ns vary across endpoints at either 78 weeks or 52 weeks.

†Sub-study for EMERGE and ENGAGE – not full population.

Table D11. Efficacy Outcomes II: Key Trials

		Timepoint /N	EMERGE (302)[75,25]			ENGAGE (301)[75,25]			Phase IB (PRIME 103)#[25,27,77,78]	
			Placebo	Low Dose	High Dose	Placebo	Low Dose	High Dose	Placebo	High Dose (10 mg/kg)
Baseline N			**548**	**543**	**547**	**545**	**547**	**555**	**48**	**32**
Adjusted Mean Change from Baseline (SE)§	**CDR-SB**		**ITT Population**							
		N	531	512	513	522	529	532	44	28
		26 Weeks	*0.64 (0.05)*	*0.48 (0.06)*	*0.56 (0.08)*	*0.53 (0.06)*	*0.48 (0.07)*	*0.59 (0.06)*	*0.84 (0.34)*	*0.74 (0.34)*
		N	429	420	432	455	454	448	39	23
		50 Weeks	*1.09 (0.09)*	*0.9 (0.08)*	*0.96 (0.08)*	*0.88 (0.08)*	*0.86 (0.08)*	*0.96 (0.08)*	54 weeks: 1.89 (0.35)	54 weeks: 0.63 (0.446)
		N	288	290	299	333	331	295	23	14
		78 Weeks	1.74 (0.12)	1.47 (0.12)	1.35 (0.12)*	1.56 (0.11)	1.38 (0.11)	1.59 (0.11)	*2.34 (0.48)*	*1.63 (0.62)*
		N	NR	NR	NR	NR	NR	NR	13	9
		222 Weeks	NR	NR	NR	NR	NR	NR	*6.97 (1.23)*	*3.87 (1.43)*
			Post-PV4							
		N	293	280	271	236	251	276	NA	NA
		26 Weeks	0.71 (0.09)	0.52 (0.09)	0.57 (0.11)	0.57 (0.1)	0.62 (0.1)	0.54 (0.09)	NA	NA
		N	74	76	80	66	82	69	NA	NA
		78 Weeks	1.74 (0.21)	1.33 (0.20)	1.22 (0.20)	1.80 (0.19)	1.44 (0.2)	1.31 (0.22)	NA	NA
	MMSE	**26 Weeks**	*-1.71 (0.15)*	*-1.72 (0.15)*	*-1.7 (0.22)*	*-2.03 (0.15)*	*-1.81 (0.16)*	*-1.91 (0.15)*	*24 weeks: -1.33 (0.51)*	*24 weeks: -0.89 (0.60)*
		50 Weeks	*-2.31 (0.18)*	*-2.27 (0.17)*	*-1.9 (0.19)*	*-2.51 (0.18)*	*-2.4 (0.19)*	*-2.49 (0.18)*	52 weeks: -2.45 (0.59)	52 weeks: -0.55 (0.74)
		78 Weeks	-3.3 (0.22)	-3.3 (0.22)	-2.7 (0.21)	-3.5 (0.21)	-3.3 (0.21)	-3.6 (0.21)	*76 weeks: -3.82 (0.76)*	*76 weeks: -1.16 (0.98)*
		220 Weeks	NR	NR	NR	NR	NR	NR	*-10.22 (0.51)*	*-4.69 (2.21)*
	ADAS-Cog 13	**26 Weeks**	*1.33 (0.27)*	*0.65 (0.32)**	*0.61 (0.25)**	*1.27 (0.26)*	*1.06 (0.24)*	*1.55 (0.26)*	NR	NR
		50 Weeks	*2.32 (0.33)*	*1.92 (0.34)*	*1.87 (0.36)*	*2.40 (0.32)*	*1.80 (0.33)*	*2.22 (0.34)*	NR	NR
		78 Weeks	5.16 (0.40)	4.46 (0.41)	3.76 (0.40)**	5.14 (0.38)	4.56 (0.38)	4.55 (0.39)	NR	NR
	ADCS-ADL-MCI	**26 Weeks**	*-1.2 (0.26)*	*-1.01 (0.25)*	*-0.60 (0.27)**	*-0.9 (0.25)*	*-0.79 (0.24)*	*-0.88 (0.26)*	NR	NR
		50 Weeks	*-2.50 (0.29)*	*-1.72 (0.33)**	*-1.9 (0.30)*	*-2.03 (0.30)*	*-1.31 (0.27)**	*-1.61 (0.28)*	NR	NR

		Timepoint /N	EMERGE (302)[75,25]			ENGAGE (301)[75,25]			Phase IB (PRIME 103)#[25,27,77,78]	
			Placebo	Low Dose	High Dose	Placebo	Low Dose	High Dose	Placebo	High Dose (10 mg/kg)
		78 Weeks	-4.3 (0.38)	-3.5 (0.38)	-2.5 (0.38)‡	-3.8 (0.35)	-3.1 (0.35)	-3.1 (0.35)	NR	NR
Adjusted Mean Change from Baseline (SE)	**Amyloid PET Composite SUVR**	**26 Weeks**	*0.006 (0.004)*	*-0.07 (0.01)‡*	*-0.08 (0.007)‡*	*-0.003 (0.001)*	*-0.067 (0.007)‡*	*-0.068 (0.007)‡*	*-0.003 (0.12)†*	*-0.20 (0.02)†*
		54 Weeks	NR	NR	NR	NR	NR	NR	0.017 (0.02)†	-0.26 (0.02)†
		78 Weeks	0.014 *(0.01)*	-0.165 *(0.01)‡*	-0.264 *(0.01)‡*	-0.003 *(0.01)*	-0.17 *(0.01)‡*	-0.24 *(0.01)‡*	NR	NR
		222 Weeks	NR	NR	NR	NR	NR	NR	*-0.26 (0.01)*	*-0.34 (0.05)*
	SUVR: Cerebellum	**54 Weeks**	NR	NR	NR	NR	NR	NR	*0.003 (0.017)*	*-0.27 (0.03)†*
	SUVR: Pons	**54 Weeks**	NR	NR	NR	NR	NR	NR	*0.01 (0.01)*	*-0.19 (0.01)†
	CSF p-tau, pg/mL	**78 Weeks**	-0.50 (4)	*-16.13 (3.5)***	*-22.88 (4.88)†*	*-2.28 (7.8)*	*-13.70 (6.8)*	*-13.3 (7.4)*	NR	NR
	CSF total tau, pg/mL	**78 Weeks**	0 (27.78)	*-87.19 (23.31)**	*-112.10 (32.89)***	*-32.68 (50.62)*	*-45.35 (45.15)*	*-103.23 (47.4)*	NR	NR
	Medial Temporal Composite	**78 Weeks**	***Pooled Data*** Placebo: 0.08 (0.02); low dose: -0.03 (0.02); high dose: -0.05 (0.02)						NR	NR
	Temporal Composite	**78 Weeks**	***Pooled Data*** Placebo: 0.08 (0.03); low dose: 0.02 (0.03); high dose: -0.01 (0.03)						NR	NR
	Frontal Composite	**78 Weeks**	***Pooled Data*** Placebo: 0.09 (0.02); low dose: 0.04 (0.02); high dose: 0.02 (0.02)						NR	NR

ADAS-Cog 13: Alzheimer's Disease Assessment Scale-Cognitive 13-Item Scale, ADCS-ADL-MCI: Alzheimer's Disease Cooperative Study-Activities of Daily Living-Mild Cognitive Impairment, CDR-SB: Clinical Dementia Rating Scale-Sum of Boxes, CSF: cerebrospinal fluid, ITT: intention-to-treat, mg/kg: milligram per kilogram, MMSE: Mini-Mental State Examination, N: total number, NA: not applicable, NR: not reported, PET: positron emission tomography, p-tau: phosphorylated tau, SE: standard error, SUVR: standard uptake value ratio

*p<0.05 ** p<0.01 † p<0.001 ‡p <0.0001.

§Ns vary across timepoints and endpoints.

#Data reported from ANCOVA analyses.

Note: Timepoints after 52 weeks for phase IB PRIME 103 are in the LTE period where the placebo arm are now placebo switchers that received 3 mg/kg or titration. Italicized data points have been digitized.

Table D12. CDR-SB Efficacy at 78 Weeks by Subgroups of Interest: EMERGE and ENGAGE

Subgroup	Arms	CDR-SB Adjusted Mean Change vs. Placebo (95% CI)					
		EMERGE (302)[25]			ENGAGE (301)[25]		
		Overall N	Overall	High Dose	Overall N	Overall	High Dose
Pre-Specified Analysis							
Baseline Clinical Stage	**MCI Due to AD**	1336	*-0.29 (-0.60, 0.04)*	-0.28 (-0.63, 0.02)	1325	NR	-0.02 (-0.32, 0.30)
	Mild AD	302	*-0.95 (-1.88, -0.02)*	-0.93 (-1.85, -0.02)	322	NR	0.27 (-0.52, 1.10)
APOE ε4 Status	**APOE ε4 Carrier**	1095	*-0.51 (-0.90, -0.12)*	0.54 (SE: 0.19)	1145	NR	-0.07 (SE: 0.18)
	APOE ε4 Non-Carrier	537	*-0.04 (-0.59, 0.48)*	0.07 (SE: 0.27)	499	NR	0.07 (SE: 0.27)
AD Medication Use	**Yes**	567	NR	-0.36 (-0.80, 0.08)	NR	NR	NR
	No	528	NR	-0.44 (-0.85, -0.02)	NR	NR	NR
Post-Hoc Analysis							
Aducanumab Dosage	**0 Doses of 10 mg/kg**	NR	*-0.05 (-0.86, 0.80)*	NR	NR	*0.06 (-0.52, 0.73)*	NR
	1-7 Doses of 10 mg/kg	NR	*-0.54 (-1.07, 0.001)*	NR	NR	*0.32 (-0.25, 0.89)*	NR
	≥8 Doses of 10 mg/kg	NR	*-0.48 (-0.97, 0.001)*	NR	NR	*-0.63 (-1.16, -0.11)*	NR
Pre and Post PV4 by APOE ε4 Status (OTC Population)*	**Pre-PV4 APOE ε4 Non-Carrier**	75/84	*-0.21 (-0.94, 0.49)*	NR	66/78	*-0.05 (-0.7, 0.59)*	NR
	Post-PV4 APOE ε4 Carrier	56/65	*-0.48 (-1.28, 0.31)*	NR	48/58	*-0.41 (-1.19, 0.42)*	NR
	Post-PV4 APOE ε4 Non-Carrier	29/31	*-0.38 (-1.44, 0.68)*	NR	23/25	*-1.01 (-2.23, 0.22)*	NR
	Weighted Mean	160/180	*-0.35 (-0.83, 0.13)*	NR	137/161	*-0.40 (-0.88, 0.11)*	NR
With and Without Rapid Progressors	**Primary: Low Dose**	543	*-0.26 (-0.57, 0.04)*	NA	547	*-0.19 (-0.47, 0.11)*	NA
	Excluding Rapid Progressors: Low Dose	539	*-0.29 (-0.57, -0.002)*	NA	542	*-0.19 (-0.44, 0.06)*	NA
	Primary: High Dose	547	NA	*-0.39 (-0.70, -0.10)*	555	NA	*0.026 (-0.26, 0.32)*
	Excluding Rapid Progressors: High Dose	542	NA	*-0.42 (-0.71, -0.14)*	546	NA	*-0.10 (-0.35, 0.16)*

AD: Alzheimer's disease, APOE ε4: apolipoprotein E ε4**,** CDR-SB: Clinical Dementia Rating Scale-Sum of Boxes, MCI: mild cognitive impairment, N: total number, NA: not applicable, NR: not reported, OTC: opportunity to complete (Week 78), PV4: Protocol Version 4

Note: Italicized data points are digitized estimates.

*Pre-PV4 ApoE carrier cohort not included as they did not have opportunity to receive 14 full doses of 10 mg/kg. (n/N: n=participants at week 78 and N=participants at baseline).

Table D13. CDR-SB at 78 Weeks Across Different Populations[25]

	Baseline N for ITT	CDR-SB at Week 78							
		ITT		Uncensored ITT		OTC		Post-PV4	
		Difference vs. Placebo (%), (95% CI); p-value		Difference vs. Placebo (%), p-value		Difference vs. Placebo (%), p-value		Difference vs. Placebo (%), (95% CI)	
EMERGE[75]	548	Placebo Decline (n=288)	1.74	Placebo Decline (n=408)	1.79	Placebo Decline (n=288)	1.61	Placebo Decline (n=304)	1.76
	543	Low Dose (n=290)	-0.26 (-15), (-0.57, 0.04); 0.09	Low Dose (n=399)	-0.22 (-12), 0.13	Low Dose (n=290)	-0.27 (-17), 0.12	Low Dose (n=295)	-0.42 (-24), (-0.94, 0.10)
	547	High Dose (n=299)	-0.39, (-22), (-0.69, -0.09); 0.01	High Dose (n=403)	-0.44 (-25), 0.003	High Dose (n=403)	-0.36 (-22), 0.04	High Dose (n=288)	-0.53 (-30), (-1.05, -0.02)
ENGAGE[75]	545	Placebo Decline (n=333)	1.56	Placebo Decline (n=414)	1.60	Placebo Decline (n=332)	1.46	Placebo Decline (n=247)	1.79
	547	Low Dose (n=331)	-0.18 (-12), (-0.47, 0.11); 0.23	Low Dose (n=421)	-0.20 (-13), 0.15	Low Dose (n=331)	-0.12 (-8), 0.45	Low Dose (n=261)	-0.35 (-20), (-0.88, 0.18)
	555	High Dose (n=295)	0.03 (2), (-0.26, 0.33); 0.83	High Dose (n=398)	-0.08 (-5), 0.59	High Dose (n=293)	0.08 (5), 0.63	High Dose (n=282)	-0.48 (-27), (-1.02, 0.06)

CDR-SB: Clinical Dementia Rating Scale-Sum of Boxes, ITT: intention-to-treat, n: number, N: total number, OTC: opportunity to complete, PV4: Protocol Version 4, 95% CI: 95% confidence interval

Table D14. Pooled Aducanumab Safety Data for Phase III EMERGE and ENGAGE at 78 Weeks [25,27]

		Patients, n (%)				
		Placebo (N=1087)	ADU 3 mg/kg (N=760)	ADU 6 mg/kg (N=405)	ADU 10 mg/kg (N=1033)	Total for ADU Arms (N=2198)
AE		945 (86.9)	700 (92.1)	347 (85.7)	946 (91.6)	1993 (90.7)
Study Drug-Related AE		273 (25.1)	373 (49.1)	148 (36.5)	530 (51.3)	1051 (47.8)
Serious AE		151 (13.9)	105 (13.8)	54 (13.3)	141 (13.6)	300 (13.6)
Serious Study Drug-Related AE		8 (0.7)	9 (1.2)	7 (1.7)	21 (2.0)	37 (1.7)
Deaths		5 (0.5)	3 (0.4)	0 (0)	8 (0.8)	11 (0.5)
AE Severity	**Mild**	445 (40.9)	252 (33.2)	122 (30.1)	331 (32.0)	705 (32.1)
	Moderate	408 (37.5)	328 (43.2)	177 (43.7)	465 (45.0)	970 (44.1)
	Severe	92 (8.5)	120 (15.8)	48 (11.9)	150 (14.5)	318 (14.5)
AE Leading to Study Drug Discontinuation		45 (4.1)	65 (8.6)	45 (11.1)	91 (8.8)	201 (9.1)
AE Leading to Study Discontinuation		31 (2.9)	32 (4.2)	27 (6.7)	38 (3.7)	97 (4.4)
AE Leading to Study Drug Discontinuation Due to ARIA		6 (0.6)	47 (6.2)	21 (5.4)	64 (6.2)	132 (6.1)
Headache		165 (15.2)	161 (21.2)	58 (14.3)	212 (20.5)	431 (19.6)
Fall		128 (11.8)	105 (13.8)	50 (12.3)	155 (15.0)	310 (14.1)
Diarrhea		74 (6.8)	62 (8.2)	27 (6.7)	92 (8.9)	181 (8.2)

ADU: aducanumab, AE: adverse event, ARIA: amyloid-related imaging abnormalities, mg/kg: milligram per kilogram, n: number, N: total number

Table D15. Pooled Aducanumab ARIA Safety Data for EMERGE and ENGAGE at 78 Weeks [25,27]

		Patients, n (%)				
		Placebo (N=1076)	ADU 3 mg/kg (N=756)	ADU 6 mg/kg (N=392)	ADU 10 mg/kg (N=1029)	Total for ADU Arms (N=2177)
ARIA-E or ARIA-H		111 (10.3)	274 (36.2)	104 (26.5)	425 (41.3)	803 (36.9)
ARIA-E		29 (2.7)	223 (29.3)	83 (20.5)	362 (35.0)	668 (30.4)
Serious ARIA-E		1 (<0.1)	6 (0.8)	3 (0.7)	13 (1.3)	22 (1.0)
ARIA-E, n/N (%)	**APOE ε4 Carrier**	16/742 (2.2)	NR	NR	290/674 (43.0)	NR
	APOE ε4 Non-Carrier	13/334 (3.9)	NR	NR	72/355 (20.3)	NR
ARIA-E by Symptomatic Status, n/N (%)	**Asymptomatic**	26/29 (89.7%)	NR	NR	268/362 (74.0)	NR
	Symptomatic	3/29 (10.3)	NR	NR	94/362 (26.0)	NR
ARIA-H		94 (8.7)	193 (25.5)	63 (16.1)	291 (28.3)	547 (25.1)
ARIA-H Microhemorrhage		71 (6.6)	141 (18.6)	50 (12.3)	197 (19.1)	388 (17.7)
ARIA-H Macrohemorrhage		4 (0.4)	1 (0.1)	3 (0.8)	3 (0.3)	7 (0.3)
ARIA-H Superficial Siderosis of CNS		24 (2.2)	91 (12.0)	23 (5.9)	151 (14.7)	265 (12.2)
AE Leading to Study Drug Discontinuation Due to ARIA		6 (0.6)	47 (6.2)	21 (5.4)	64 (6.2)	132 (6.1)

ADU: aducanumab, AE: adverse event, APOE ε4: apolipoprotein E ε4, ARIA: amyloid-related imaging abnormalities, ARIA-E: amyloid-related imaging abnormalities-edema/effusion, ARIA-H: amyloid-related imaging abnormalities-hemorrhage or superficial siderosis, CNS: central nervous system, mg/kg: milligram per kilogram, n: number, N: total number, NR: not reported

Table D16. ARIA Symptomatic Status by Arm for EMERGE and ENGAGE

		EMERGE (302)[75]			ENGAGE (301)[75]		
Study Arms		**Placebo**	**Low Dose**	**High Dose**	**Placebo**	**Low Dose**	**High Dose**
N		544	537	541	533	544	554
Any ARIA (either E or H), n (%)		56 (10.3)	176 (32.8)	223 (41.2)	52 (9.8)	167 (30.7)	223 (40.3)
Symptomatic Status, n/N (%)	**Asymptomatic ARIA**	53/56 (94.6)	138/176 (78.4)	179/223 (80.3)	49/52 (94.2)	139/167 (83.2)	158/223 (70.9)
	Symptomatic ARIA	3/56 (5.4)	38/176 (21.6)	44/223 (19.7)	3/52 (5.8)	28/167 (16.8)	65/223 (29.1)

ARIA: amyloid-related imaging abnormalities, E: edema/effusion, H: hemorrhage or superficial siderosis, n: number, N: total number

Table D17. Safety Data for Phase I Studies

		Phase IB (PRIME 103)[79]		Phase I (101)[74]		
Study Arms		**Placebo Switchers***	**10 mg/kg**	**Placebo**	**10 mg/kg**	**Total†**
Timepoint		**48 Months**		**24 Weeks**		
N		37	32	14	6	39
Any AEs, n (%)		37 (100)	29 (91)	5 (36)	4 (67)	21 (54)
Serious AEs, n (%)		21 (57)	16 (50)	0 (0)	0 (0)	3 (8)
AEs Leading to Discontinuation, n (%)		11 (30)	16 (50)	0 (0)	0 (0)	0 (0)
Discontinuation due to ARIA, n (%)		5 (14)	9 (28)	0 (0)	0 (0)	0 (0)
All Cause Deaths, n (%)		1 (3)	2 (6)	0 (0)	0 (0)	0 (0)
Headache, n (%)		10 (27)	13 (41)	2 (14)	0 (0)	8 (21)
Nasopharyngitis, n (%)		6 (16)	4 (13)	NR	NR	NR
Fall, n (%)		9 (24)	6 (19)	NR	NR	NR
ARIA Safety						
N		46	32	14	6	39
Any ARIA (either E or H), n (%)		3 (6)	15 (47)	0 (0)	0 (0)	3 (8)
Symptomatic Status, n/N (%)	**Asymptomatic ARIA**	3/8 (38)	8/13 (62)	0 (0)	0 (0)	0 (0)
	Symptomatic ARIA	5/8 (63)	5/13 (38)	0 (0)	0 (0)	3 (8)
ARIA-E, n/total (%)	**APOE ε4 Carriers**	7/25 (28)	11/20 (55)	0 (0)	0 (0)	1 (3)
	APOE ε4 Non-Carriers	1/12 (8)	2/12 (17)	0 (0)	0 (0)	2 (5)
ARIA-H, n (%)	**Microhemorrhage**	2 (5)	2 (6)	0 (0)	0 (0)	1 (3)
	Superficial Siderosis			0 (0)	0 (0)	0 (0)
	Macrohemorrhage			0 (0)	0 (0)	0 (0)

APOE ε4: apolipoprotein E ε4, ARIA: amyloid-related imaging abnormalities, ARIA-E: amyloid-related imaging abnormalities-edema/effusion, ARIA-H: amyloid-related imaging abnormalities-hemorrhage or superficial siderosis, E: edema, H: hemorrhage or superficial siderosis, mg/kg: milligram per kilogram, n: number, N: total number

*Placebo switchers: received 3 mg/kg or titration in LTE period.

†The three cases of ARIA-E reported were in patients who received 60 mg/kg and were determined to be serious.

Table D18. Study Quality

Trial	Comp. Groups	Non-Differential Follow-Up	Patient/Investigator Blinding (Double-Blind)	Clear Definition of Intervention	Clear Definition of Outcomes	Selective Outcome Reporting*	Measurements Valid	Intention to Treat Analysis	Approach to Missing Data
Phase III EMERGE	Yes	Yes	Uncertain	Yes	Yes	Yes	Yes	Yes	MMRM
Phase III ENGAGE	Yes	Yes	Uncertain	Yes	Yes	Yes	Yes	Yes	MMRM
Phase IB PRIME	Yes	Yes	Uncertain	Yes	Yes	Yes	Yes	No†	MMRM

Comp.: comparable, MMRM: mixed model repeated measures

*Publications are not yet peer-reviewed and are considered grey literature.

†Efficacy analysis population: all participants who were randomized, received at least one dose of study treatment, and had both baseline and at least one post-baseline CDR or MMSE assessment for at least one scheduled timepoint.

D5. Ongoing Studies

Table D19. Ongoing Studies

Title/Trial Sponsor	Study Design	Treatment Arms	Patient Population	Primary Outcomes	Estimated Completion Date
Phase IIIb Open-Label, Multicenter, Safety Study of BIIB037 (Aducanumab) in Subjects With AD Who Had Previously Participated in Aducanumab Studies 221AD103, 221AD301, 221AD302 and 221AD205 (EMBARK) NCT04241068 Sponsor: Biogen	Phase IIIb OL, MC Study Estimated enrollment: 2,400	10 mg/kg aducanumab IV every 4 weeks for a total of 100 weeks	**Inclusion Criteria** • Participation in an aducanumab clinical study at time of announcement of early termination **Exclusion Criteria** • Medical or neurological condition (other than AD) that might be contributing to cognitive impairment • Stroke or any unexplained loss of consciousness within 1 year prior to screening • Clinically significant unstable psychiatric illness in past 6 months • History of unstable angina, MI, advanced chronic heart failure • Contraindications to brain MRI	• Number of participants with AE and serious AE (up to week 118) • Number of participants with AEs leading to treatment discontinuation or study withdrawal (up to week 118) • Number of participants with ARIA-E, ARIA-H, and antidrug antibodies in serum (up to week 102)	October 2023

AD: Alzheimer's disease, AE: adverse event, ARIA-E/H: amyloid-related imaging abnormalities edema/effusion or hemorrhage, IV: intravenous, MC: multi-center, mg/kg: milligram per kilogram, M: myocardial infarction, OL: open-label

Source: www.ClinicalTrials.gov (NOTE: studies listed on site include both clinical trials and observational studies).

D6. Assessment of Publication Bias

As described in our methods, we searched for studies that would have met our inclusion criteria, and for which no findings have been published to evaluate the presence of potential publication bias. The aducanumab clinical development program was suspended in early 2019 due to results from a prespecified interim analysis for futility in the two pivotal phase III trials, EMERGE and ENGAGE. We identified three trials that were either terminated based on the futility analysis or were completed but have not been made public. These included two Phase I trials (102 and 104), which were completed in 2016, and the Phase II EVOLVE study, which was terminated in 2019 alongside the other aducanumab trials due to the futility analysis. We have summarized the key study design information we have for these three studies in Table D20 on the following page.

Table D20. Unpublished Aducanumab Trials

Trial Name NCT	Study Design	Population (N)	Intervention Arms / Dosing Schedule	Primary Outcomes	Inclusion/Exclusion Criteria	Status
Phase I 102 NCT02782975	OL, randomized, bioavailability study	Healthy individuals (N=28)	Single dose of ADU (6 mg/kg IV or 420 mg SC)	Pharmacokinetic parameters	***Inclusion Criteria*** • Healthy individuals (minimum weight of 45 kg, in good health) ***Exclusion Criteria*** • MMSE score <27 at screening • History of clinically significant cardiac, endocrinologic, hematologic, etc. disease • History of severe allergic or anaphylactic reactions or malignant disease	Completed 2016 (could not locate full text) Last update on Clinical Trials: 2017
Phase I SAD/MAD (JP) 104 NCT02434718	DB, PC, randomized single and multiple ascending dose om Japanese participants	Mild-to-moderate AD (N=21)	Single and multiple doses of 1 or 3 mg/kg; 6 mg/kg after titration; 10 mg/kg after titration or PBO in 4:1 ratio	**[Up to week 42]** Incidence of AE/SAE Clinically significant changes in vital signs and 12-lead ECG data, abnormalities in neurological and physical exams Brain MRI findings to assess ARIA, including ARIA-E and H	***Inclusion Criteria*** • Clinical diagnosis of mild-to-moderate AD ***Exclusion Criteria*** • Medical or neurological condition of than AD that may be a contributing cause of dementia • TIA or stroke or any unexplained loss of consciousness within 1 year of screening • Poorly controlled diabetes mellitus • History of unstable angina, MI, chronic heart failure	Completed 2016 (could not locate full text) Last update on Clinical Trials: 2020
Phase II EVOLVE 205 NCT03639987	Parallel group, DB, MC, RCT with an LTE period	MCI due to AD and mild AD dementia (N=52)	**Group 1** 1. ADU IV every 4 weeks up to week 52 2. Placebo **Group 2**	Number of clinically impactful ARIA [baseline to week 54]	***Inclusion Criteria*** • Must have positive PET scan with evidence of cerebral Aβ accumulation • Consent to ApoE genotyping • Meet clinical criteria for MCI due to AD or mild AD dementia according to NIA-AA criteria	Terminated (study discontinued based on futility analysis conducted on Phase III trials)

Trial Name NCT	Study Design	Population (N)	Intervention Arms / Dosing Schedule	Primary Outcomes	Inclusion/Exclusion Criteria	Status
			1. ADU IV every 4 weeks up to week 52.		***Exclusion Criteria*** • Any uncontrolled medical or neurological/neurodegenerative condition (other than AD) that might be a contributing cause of the participant's cognitive impairment • Clinically significant unstable psychiatric illness within 6 months prior to screening	

AD: Alzheimer's disease, AE: adverse event, APOE: apolipoprotein E, ARIA-E/H: amyloid-related imaging abnormalities edema/effusion or hemorrhage, DB: double-blind, ECG: electrocardiogram, IV: intravenous, LTE: long term extension, MC: multicenter, MCI: mild cognitive impairment, MI: myocardial infarction, MMSE: mini mental state exam, mg/kg: milligram per kilogram, MRI: magnetic resonance imaging, NIA-AA: National Institute on Aging And Alzheimer's Association, OL: open-label, PBO: placebo, PET: positron emission tomography, RCT: randomized controlled trial, SAE: serious adverse event, SC: subcutaneous

D7. Previous Systematic Reviews and Technology Assessments

We identified one ongoing health technology assessment (HTA) conducted by NICE and one previously conducted systematic literature review (SLR) evaluating the effect of amyloid reduction on cognitive decline. Both are briefly summarized below.

NICE

Aducanumab for treating mild cognitive impairment in early Alzheimer's disease [ID3763]

NICE is currently conducting an appraisal of the clinical and cost effectiveness of aducanumab for the treatment of MCI in early AD. As of September 2020, only the draft scope has been posted. The expected publication date is May 25, 2022.

Systematic Literature Review

Ackley, S.F., et al. (2021). "Effect of Reductions in Amyloid Levels on Cognitive Change in Randomized Trials: Instrumental Variable Meta-Analysis."[29]

Investigators conducted a meta-analysis using trials of drugs to treat AD to assess the effects of amyloid reduction on cognitive change. A literature search was conducted to identify trials that reported change in brain amyloid levels reported by amyloid PET and a change in one or more cognitive test score for each randomization arm in the trial. Fourteen RCTs for eight different amyloid-targeting drugs were included in the meta-analysis. The drugs included were bexarotene, solanezumab, LY450139, gantenerumab, bapineuzumab, verubecestat, BAN2401, and aducanumab. Adults ages 50 years or older, who were amyloid positive at baseline and were diagnosed with MCI or AD were included. Brain amyloid was measured using the SUVR and cognition was measured by change in MMSE scores. Investigators used instrumental variable analyses to observe the effects of amyloid-reducing drugs on amyloid level changes, and subsequently to evaluate the effect of amyloid level reduction on cognitive decline.

On average, study drugs reduced PET SUVR by 0.1 units, and the estimate of MMSE change associated with this 0.1 reduction in amyloid was 0.03 (95% CI: -0.06 to 0.01), indicating that amyloid level changes had little to no effect on cognitive change. This conclusion aligns with the findings from assessing the effect of amyloid level reduction on cognition in individual trials. In this analysis, only one trial, Biogen's EMERGE trial for aducanumab, had a statistically significant effect when utilizing the CDR-SB as the endpoint rather than MMSE. These findings suggest that reducing amyloid levels does not significantly improve cognition or slow cognitive decline. Investigators identified limitations in their meta-analysis, which include lack of available data from additional trials, the assumption that amyloid-targeting drugs would not affect cognition through any other means than through amyloid reduction, the use of only MMSE to encapsulate the measure of

cognitive change, errors in data inputting, and lack of consideration for potential confounders affecting both amyloid levels and cognitive decline.

E. Long-Term Cost Effectiveness: Supplemental Information

E1. Detailed Methods

Table E1. Impact Inventory

Sector	Type of Impact (Add Additional Domains, as Relevant)	Included in This Analysis from […] Perspective?		Notes on Sources (if Quantified), Likely Magnitude and Impact (if Not)
		Health Care Sector	Societal	
Formal Health Care Sector				
Health Outcomes	Longevity effects	X	X	
	Health-related quality of life effects	X	X	
	Adverse events	X	X	
Medical Costs	Paid by third-party payers	X	X	
	Paid by patients out-of-pocket	☐	☐	
	Future related medical costs	X	X	
	Future unrelated medical costs	X	X	
Informal Health Care Sector				
Health-Related Costs	Patient time costs	N/A	☐	
	Unpaid caregiver-time costs	N/A	X	
	Transportation costs	N/A	☐	
Non-Health Care Sector				
Productivity	Labor market earnings lost	N/A	X	
	Cost of unpaid lost productivity due to illness	N/A	☐	
	Cost of uncompensated household production	N/A	☐	
Consumption	Future consumption unrelated to health	N/A	☐	
Social Services	Cost of social services as part of intervention	N/A	☐	
Legal/Criminal Justice	Number of crimes related to intervention	N/A	☐	
	Cost of crimes related to intervention	N/A	☐	
Education	Impact of intervention on educational achievement of population	N/A	☐	
Housing	Cost of home improvements, remediation	N/A	☐	
Environment	Production of toxic waste pollution by intervention	N/A	☐	
Other	Other impacts (if relevant)	N/A	☐	

N/A: not applicable

Adapted from Sanders et al.[80]

Target Population

The model focused on a cohort of patients with MCI due to AD or mild AD entering the model that mirrored the characteristics from the two Phase III trials. Age influenced mortality and quality of life; sex influenced mortality. Weight factored into weight-based dosing for aducanumab, and the baseline clinical stage and setting of care determined which health state and setting of care an individual started the model in. Baseline patient characteristics are detailed in Table E2.

Table E2. Baseline Population Characteristics

Patient Characteristics	Value	Source	Notes
Mean Age	70	Budd Haeberlein et al., 2019[28]	Weighted average of participants in ENGAGE and EMERGE
Percent Female, %	52%	Budd Haeberlein et al., 2019[28]	Weighted average of participants in ENGAGE and EMERGE
Weight, kg	73.7	Biogen data on file[34]	Biogen analysis of National Institute on Aging National Alzheimer's Coordinating Center 2015-2020 data
Clinical Stage, % **MCI Due to AD** **Mild AD**	 55% 45%	Potashman et al., 2020[81]	AD population with underlying beta-amyloid pathology
Setting of Care, % **Community** **Long-Term Care**	 92% 8%	Johnson, 2019[82]	Percent of population ages 65-74 who received long-term services and supports

AD: Alzheimer's disease, kg: kilogram, MCI: mild cognitive impairment

E2. Model Inputs and Assumptions

This section details the value and associated source for each model input that informed the cost-effectiveness model as well as details around additional model choices and assumptions.

Table E3. Key Model Choices and Assumptions

Model Choice or Assumption	Rationale
Aducanumab discontinuation due to adverse events (i.e., ARIA) occurred within the first 18 months of treatment initiation.	Over the trial time horizon, treatment discontinuation due to adverse events was approximately the same as the probability of symptomatic ARIA. ARIA has been observed as an adverse event for many studied treatments that target aggregated beta-amyloid. Consistent findings across these studies suggest ARIA occurs early in the treatment course. Discontinuation not related to adverse events (e.g., upon transition to severe AD) occurred over the model time horizon.
Caregiver impacts were incorporated in the societal perspective.	The health care system perspective included the patient's cost and outcomes.
Long-term care costs were incorporated in the health care system perspective.	The health care system perspective included the cost and outcomes of the patient.
Caregiver impacts were modeled as if each patient had one primary caregiver.	Evidence on caregiver impacts has been collected from a single, primary caregiver.

AD: Alzheimer's disease, ARIA: amyloid-related imaging abnormality

Clinical Inputs

Transition Probabilities between Alive Health States

Table E4 provides the annual transition probabilities between each of the alive health states. These estimates are from a recent analysis of AD progression using data from beta-amyloid positive patients in the National Alzheimer's Coordinating Center database.[83] Due to differences in age and sex (two characteristics that influence mortality) between the sample from the National Alzheimer's Coordinating Center and our baseline population characteristics described above, we calculated probabilities of transitioning to each health state conditioned on if an individual was alive. The calculation of these conditional probabilities normalizes the annual transition probabilities to be applied to our modeled population. The annual transition probabilities reported in Table E4 are the conditional probabilities and will be applied given the individual does not die in the model cycle.

Table E4. Annual Health State Transition Probabilities Given Individual Does Not Die in Cycle

	MCI Due to AD	Mild AD	Moderate AD	Severe AD	Source
MCI Due to AD	77%	23%	0%	0%	Potashman et al., 2020[83]
Mild AD	3%	58%	35%	4%	
Moderate AD	0%	3%	55%	42%	
Severe AD	0%	0%	2%	98%	

AD: Alzheimer's disease, MCI: mild cognitive impairment

Mortality

For each cycle, a risk of death was assigned based on age, sex, and health state occupancy. Age and sex-adjusted mortality was the foundation for transitions to the dead health state, with an increased risk of death associated with AD that is dependent on the severity of AD. Age- and sex-adjusted mortality was sourced from the Human Mortality Database US-specific tables.[84] Table E5 provides the relative risks of death from each health state. These relative risks were multiplied to the age- and sex-adjusted mortality for each model cycle.

Table E5. Relative Risk of Death Based on Severity of Dementia

	Value	Source	Notes
MCI Due to AD	1.82	Andersen et al., 2010[85]	Multiplied by age- and sex-adjusted all-cause mortality
Mild AD	2.92		
Moderate AD	3.85		
Severe AD	9.52		

AD: Alzheimer's disease, MCI: mild cognitive impairment

Progression to Long-Term Care

Specific to each health state, the model also tracked the setting of care (e.g., community or long-term care). Patients could progress from community to long-term care; however, once in long-term care, they remained there until death. The annual probabilities of progressing to long-term care specific to each alive health state are described in Table E6 below. These estimates are from an analysis that used Consortium to Establish a Registry for Alzheimer's Disease data.[32]

Table E6. Annual Transition Probabilities to Long-Term Care

	Value	Source
MCI Due to AD	2.4%	Calculated based on the reported mild AD annual transition probability and relationship between relative risk of death for MCI due to AD and mild AD
Mild AD	3.8%	Neumann et al., 1999[32]
Moderate AD	11.0%	
Severe AD	25.9%	

AD: Alzheimer's disease, MCI: mild cognitive impairment

Aducanumab Treatment Effectiveness

We assumed that, to the extent it is effective, aducanumab reduced disease progression from the MCI due to AD and from mild AD health states. We used best available evidence from intention to treat analyses, consistent with evidence from Section 3 of this report, to estimate the effect of aducanumab on reducing disease progression for these health state transitions. The published evidence on aducanumab efficacy included the placebo and aducanumab change in CDR-SB over time. Although change in CDR-SB is a clinically important measure, what is most relevant to the model is looking at rates of transitions among health states. The manufacturer of aducanumab provided us the hazard ratio for the MCI to mild AD transition using evidence from the EMERGE trial (provided as academic-in-confidence at this time); however, they did not provide us the hazard ratio for the MCI to mild AD transition from the ENGAGE trial. Without a hazard ratio for the ENGAGE trial, we assumed the hazard ratio would be equivalent to the relative percent difference in CDR-SB change over time between the aducanumab and placebo arm. Table E7 presents the hazard ratios applied to transitions out of MCI due to AD in the model pathway that included aducanumab. The aducanumab efficacy used in the base-case analysis was calculated as a weighted average (based on the sample sizes) of the results from the two pivotal trials (ENGAGE and EMERGE). Due to the inconsistencies observed between the two trials and the insufficiency of the current evidence, we also present potential conservative treatment benefit and optimistic treatment benefit analyses as scenario analyses, which are largely driven by different aducanumab effectiveness assumptions.

Table E7. Aducanumab Effectiveness on Transitions Out of MCI due to AD

ITT Analysis	Hazard Ratio	Source	Notes
EMERGE	0.69	Biogen data on file[34]	N/A
ENGAGE	1.02	Budd Haeberlein et al., 2019[28]	Assumed equivalent to percent difference in CDR-SB change over time between aducanumab and placebo arm
Weighted Average	0.86	Calculated	Weighted average based on trials' sample size

CDR-SB: Clinical Dementia Rating-Sum of Boxes, ITT: intention-to-treat, MCI: mild cognitive impairment, N/A: not applicable

*The percent difference compares the aducanumab change to the placebo change in CDR-SB.

Due to the clinical characteristics and early disease stages of the trial participants, the evidence on health state transitions was from the MCI heath state to the mild AD health state. To our knowledge, there is limited efficacy evidence on the mild AD to moderate AD health state transition. Stakeholders suggested there is likely no effect at reducing disease progression once a patient has reached moderate AD, and thus we assumed a hazard ratio of 1.0 for transitions out of moderate AD. To estimate the effectiveness in the mild AD health state, we assumed the

effectiveness in the mild AD health state would be somewhere between the effectiveness for the MCI health state and the absence of effect at reducing disease progressions assumed in the moderate AD health state. We thus assumed the effectiveness in the mild AD health state to be the midpoint of those numbers – half of the effectiveness in the MCI health state. This assumption was extensively tested through sensitivity analyses.

Adverse Events

An important adverse event associated with aducanumab is the occurrence of ARIA, of which two main forms exist: ARIA-E and ARIA-H. ARIA typically occurs early in the treatment course and is often not associated with any symptoms.[35] Table E8 presents the probability and average duration of ARIA events. Later sections of this supplement detail how the occurrence of these events influence treatment continuation, cost, and quality of life. Costs and disutilities for ARIA were not duplicated if an individual experienced ARIA-E and ARIA-H concurrently. In essence, those who experienced both had the same disutility and cost as those who experienced one at any given time due to the same disutility and monitoring required of ARIA-E and ARIA-H.

Table E8. Adverse Events

Parameter	Aducanumab	Source
Probability of ARIA-E	30.7%	FDA Advisory Committee Briefing Document[35]
Probability of ARIA-H	25.1%	
Concurrent ARIA-E and ARIA-H	17.9%	
Probability of Symptomatic ARIA	10%	
Duration of ARIA	12 weeks	

ARIA: amyloid-related imaging abnormality, FDA: Food and Drug Administration

Discontinuation

Evidence on discontinuation due to adverse events from ENGAGE and EMERGE were used to estimate discontinuation due to adverse events over the first 18 months. No discontinuation due to adverse events was assumed after the trial time horizon due to consistent findings that ARIA occurs at the beginning of the treatment course.[35] Treatment discontinuation rates due to adverse events, as a weighted average of the treatment discontinuation due to adverse events reported in both pivotal trials, are presented in Table E9. In addition to discontinuation due to adverse events that occurred within the first 18 months of treatment initiation, patients continued to discontinue aducanumab treatment each year due to disease progression (i.e., patients discontinued treatment when they entered the severe AD health state).

Table E9. Aducanumab Treatment Discontinuation

Parameter	Aducanumab	Source
Treatment Discontinuation Due to Adverse Events	10%	FDA Advisory Committee Briefing Document[35]
Treatment Discontinuation Not Related to Adverse Events	Dependent on health state transitions, but average 9% per year	Potashman et al., 2020[83]

FDA: Food and Drug Administration

Utility Inputs

Health state utilities were derived from publicly available literature. These utility estimates primarily came from a cross-sectional study of AD patients and caregivers with stratifications for both disease severity and setting of care.[36] The utility weights were derived from the Health Utilities Index Mark II with weights based on the standard-gamble approach.[36] The HUI:2 is a commonly used instrument to calculate utility weights in the AD population because cognition is a separate attribute. The caregivers served as proxy respondents for the patient's quality of life, but also assessed their own quality of life.[36] Responses from the HUI:2 were converted to utility weights using the multi-attribute utility function developed for the HUI:2. We compared the utility estimates from this cross-sectional study to a recent systematic literature review published in 2020 and the estimates were comparable.[86] We elected not to use the recent systematic literature review estimates because the utility estimates were not stratified by care setting (e.g., community vs. long-term care) and did not report quality-of-life estimates for the caregiver of the patient.

The model used the utility estimates and the age of the patients in the cross-sectional study,[36] to calculate a disutility for each disease state and setting of care based off age-adjusted utility estimates.[87] The calculated disutility was directly used in the model and was subtracted from age-adjusted utility estimates that varied based on age for each model cycle.[87] Therefore, the model estimated quality of life that was a function of age, disease severity, and setting of care. Table E10 presents the utility estimates from the cross-sectional study. The disutilities that were calculated from these estimates are presented in the Key Model Inputs table in the report.

Table E10. Patient Utility Estimates

Parameter	Community Setting	Long-Term Care Setting	Source
MCI Due to AD	0.73	Assumed same as community	Neumann et al., 1999[36]
Mild AD	0.68	0.71	Neumann et al., 1999[32,36]
Moderate AD	0.54	0.48	
Severe AD	0.37	0.31	

AD: Alzheimer's disease, MCI: mild cognitive impairment

In addition to the health state utilities reported above, a disutility of -0.14 was applied to patients experiencing symptomatic ARIA (average duration of 12 weeks). This disutility estimate is the

disutility estimate for headache,[88] which was the most reported symptom among those with symptomatic ARIA.[35]

Caregiver disutilities were incorporated in the societal perspective. Caregiver utility estimates were calculated from the same cross-sectional study as the patient utility estimates described above.[36] The model used the utility estimates and the age of the caregivers in the cross-sectional study,[36] to calculate a disutility for each disease state and setting of care based off age-adjusted utility estimates.[87] The calculated disutility was directly used in the model and was subtracted from age-adjusted utility estimates that varied based on the age for each model cycle.[87] Therefore, the model estimated quality of life that was a function of age, disease severity, and setting of care. Table E11 presents the utility estimates from the cross-sectional study. Importantly, the utility estimates reported in the cross-sectional study did not vary by AD disease severity (i.e., did not suggest a difference in caregiver utility for if the patient had mild, moderate, or severe AD). We adjusted these estimates to account for the difference in caregiver utility among AD disease severity reported in a study by Mesterton and colleagues.[37] The disutilities that were calculated from these estimates are presented in the Key Model Inputs table in the report. The caregiver disutility was applied onto the patient's utility estimate. No caregiver disutility was assigned upon or following the patient's death.

Table E11. Caregiver Utility Estimates

Parameter	Community Setting	Long-Term Care Setting	Source
MCI Due to AD	0.88	0.88	Neumann et al., 1999[36]
Mild AD	0.86	0.86	Neumann et al., 1999[32] & Mesterton et al., 2010[37]
Moderate AD	0.83*	0.83*	
Severe AD	0.81*	0.81*	

AD: Alzheimer's disease, MCI: mild cognitive impairment

*Adjusted original utility reported in Neumann et al., 1999[36] by relationship published in Mesterton et al., 2010.[37]

Economic Inputs

All costs used in the model were updated to 2020 US dollars using methods following the ICER reference case. Costs included in the health care system perspective were costs associated with the acquisition of aducanumab, administration and monitoring of aducanumab, costs to manage adverse events, other non-aducanumab health care (medical and pharmacy) costs, and long-term care costs. Other costs included in the societal perspective included components such as patient productivity and caregiver impacts.

Drug Acquisition Costs

The following inputs were used to model drug utilization and associated costs:

- Route of administration
- Dosing (accounting for vial wastage for IV treatments)
- Frequency of administration
- Duration of treatment
- Percent of patients that receive treatment

Table E12 reports these characteristics for aducanumab.

Table E12. Treatment Regimen Recommended Dosage

Generic Name	Aducanumab
Brand Name	Aduhelm™
Manufacturer	Biogen
Route of Administration	IV
Dosing	10 mg/kg after titration over 24 weeks
Frequency of Administration	Every 4 weeks
Duration of Treatment	MCI due to AD through moderate AD
Percent of Patients that Receive	All patients in MCI through moderate AD that do not discontinue due to adverse event

AD: Alzheimer's disease, IV: intravenous, kg: kilogram, MCI: mild cognitive impairment, mg: milligram, TBD: to be determined

We used the manufacturer reported price for aducanumab in the model. Table E13 reports the drug costs assumed in the model.

Table E13. Drug Costs

Drug	Unit Cost	Annual Cost	Source
Aducanumab, Year 1*	TBD	$41,344	Manufacturer estimate[38] + 6%
Aducanumab, Years 2+	TBD	$59,360	Manufacturer estimate†[38] + 6%

TBD: to be determined

*Price is lower to account for dose titration characteristic of first year on treatment.

†The model used $56,000 per year (plus 6%) after year one based on estimates reported by the manufacturer, but the price would actually be $56,056 (plus 6%) based on the WAC and accounting for vial wastage.

Non-Drug Costs – Health Care System Perspective

Non-drug costs that were included in the health care system perspective are described below.

Administration Costs

Aducanumab is administered by way of IV administration every four weeks. We assumed an average administration cost of $74.58 per administration (HCPCS Code 96365).[89]

Monitoring Costs

While an individual is receiving aducanumab treatment, they are being monitored using brain MRI. Patients receive a brain MRI prior to initiating treatment, and then prior to infusions seven and 12. Therefore, we modeled three brain MRIs in the first year.[90] We assumed an average brain MRI cost of $255.33 per scan (HCPCS Code 70553).[89]

Adverse Event Costs

In addition to the brain MRIs described above for monitoring, if a patient experiences an ARIA event, the patient will undergo a brain MRI every four weeks until the ARIA is resolved or stabilized.[35] The average duration of an ARIA event is 12 weeks; therefore, a patient who has an ARIA event will receive three additional brain MRIs associated with managing the adverse event. We assumed an average brain MRI cost of $255.33 per scan (HCPCS Code 70553).[89]

Non-Aducanumab Health Care Costs

Annual medical costs stratified by disease severity were sourced from a study conducted by Leibson and colleagues.[91] This study reported the average annual inpatient and outpatient medical costs for patients who were cognitively normal, had MCI, were newly diagnosed with dementia, or had prevalent dementia. We assumed costs associated with the newly diagnosed dementia group corresponded to the mild AD health state, and costs associated with the prevalent dementia group corresponded to the moderate and severe AD health states. We assumed the annual medical costs were the same for patients in the community or in long-term care. Using these estimates, we calculated a cost multiplier for each health state in the model based on those that were cognitively normal. In the model, we multiplied this cost multiplier by the average age-adjusted health care costs for the US general population. These annual costs were included in the model to account for medical health care utilization, stratified by disease severity. The cost multipliers are described in Table E14.

Table E14. Direct Medical Cost Multipliers

Health State	Multiplier	Source
MCI Due to AD	1.12	Leibson et al., 2015[91]
Mild AD	1.56	
Moderate AD	1.93	
Severe AD	1.93	

AD: Alzheimer's disease, MCI: mild cognitive impairment

To capture other pharmacy costs not related to aducanumab, we assumed 33.3% of mild AD patients received generic donepezil 10 mg once daily ($0.22 per day)[92] and 33.3% of moderate AD patients received generic memantine 10 mg twice daily ($0.68 per day).[92,93]

Long-Term Care Costs

For patients in the long-term care setting, additional costs associated with long-term care were included. Table E15 lists the monthly costs for long-term care that were assigned to those individuals who progressed to the long-term care setting. The annual cost was used in the model.

Table E15. Long-Term Care Costs

Parameter	Value*	Source	Notes
Long-Term Care	$7,186 per month	Administration on Aging[94]	Skilled nursing facility cost

*Costs have been inflated from 2016 US dollars to 2020 US dollars using the price index for health care services.[95]

Additional Costs for Societal Perspective

Patient productivity costs, caregiver productivity costs, and caregiver direct medical costs were also included in the modified societal perspective.

Patient Productivity Costs

A study published in 2020 by Robinson and colleagues reported that among patients with beta-amyloid positive MCI, 20.4% reported still working, with 4.9% of those who worked reporting a reduction in work due to AD.[39] Similarly, among patients with beta-amyloid positive mild AD, 11.2% reported still working, with 8.6% of those who worked reporting a reduction in work due to AD.[39] We assumed 0% of moderate and severe AD patients work for reasons not related to AD. The average age of the population in the Robinson study was comparable to the average age of our modeled cohort. For those patients who reduced work due to AD, we assigned lost productivity costs of 20 hours per week. The average hourly wage of $29.58 was used to monetize the lost productivity.[96]

Caregiver Productivity Costs

The Robinson et al., 2020 study also reported caregiver time spent caregiving for patients with MCI.[39] A separate source by Haro and colleagues reported caregiver time spent caregiving for community-dwelling patients with mild, moderate, and severe AD.[40] Table E16 reports the average caregiver time spent caregiving for community-dwelling patients in each health state. Time included time spent providing supervision and activities of daily living (basic and instrumental). The annual time was used in the model.

Table E16. Caregiver Time Spent Caregiving for Community-Dwelling Patients

Health State	Value	Source
MCI Due to AD	69 hours per month	Robinson et al., 2020[39]
Mild AD	113 hours per month	Haro et al., 2014[40]
Moderate AD	169 hours per month	
Severe AD	298 hours per month	

AD: Alzheimer's disease, MCI: mild cognitive impairment

The What Matters Most study, sponsored by the Alzheimer's Disease Patient and Caregiver Engagement consortium, suggested caregiver time spent with long-term-care-dwelling patients was 44% that of caregiver time spent with community-dwelling patients; and thus the estimates reported were multiplied by 44% to estimate the caregiver time spent for long-term-care-dwelling patients.[41] The average hourly wage of $29.58 was used to monetize the time spent caregiving.[96]

Caregiver Direct Medical Costs

Table E17 presents the direct medical costs for the primary caregiver of a patient with AD. The Robinson and colleagues study reported these estimates for beta-amyloid positive MCI patients and beta-amyloid positive mild AD patients.[39] We estimated the caregiver direct medical costs for moderate AD and severe AD by multiplying the reported costs by Robinson and colleagues for mild AD by the relationship in disutility calculated from the study by Mesterton and colleagues.

Table E17. Caregiver Direct Medical Costs

Health State	Value	Source
MCI Due to AD	$447 per month	Robinson et al, 2020[39]
Mild AD	$938 per month	
Moderate AD	$1,501 per month	Assumption based on Robinson et al, 2020[39] & Mesterton et al., 2010[37]
Severe AD	$1,876 per month	

AD: Alzheimer's disease, MCI: mild cognitive impairment

E3. Results

Table E18. Percent On Treatment over Time Horizon

Year	Percent On Treatment	Percent Alive
Year 0	100%	100.0%
Year 1	84%	95.6%
Year 3	72%	90.3%
Year 4	58%	83.5%
Year 5	45%	75.2%
Year 6	34%	65.9%
Year 7	25%	55.9%
Year 8	17%	46.0%
Year 9	11%	36.5%
Year 10	6%	27.9%
Year 11	1%	20.6%
Year 12	0%	14.6%
Year 13	0%	10.0%
Year 14	0%	6.6%
Year 15	0%	<5%

Table E19. Undiscounted Years in Each Health State

Year	Aducanumab	Supportive Care
MCI	2.48	2.20
Mild AD	2.07	2.00
Moderate AD	1.23	1.29
Severe AD	1.61	1.71

AD: Alzheimer's disease, MCI: mild cognitive impairment

Description of evLYG Calculations

The cost per evLYG considers any extension of life at the same "weight" no matter what treatment is being evaluated. Below are the stepwise calculations used to derive the evLYG.

1. First, we attribute a utility of 0.851, the age- and gender-adjusted utility of the general population in the US that are considered healthy.[97]
2. For each cycle (Cycle I) in the model where using the intervention results in additional years of life gained, we multiply this general population utility with the additional life years gained (ΔLYG).
3. We sum the product of the life years and average utility (cumulative LYs/cumulative QALYs) for Cycle I in the comparator arm with the value derived in Step 2 to derive the equal value of life years (evLY) for that cycle.
4. If no life years were gained using the intervention versus the comparator, we use the conventional utility estimate for that Cycle I.

5. The total evLY is then calculated as the cumulative sum of QALYs gained using the above calculations for each arm.
6. The evLY for the comparator arm was equivalent to the QALY estimate for that model cycle.

Finally, the evLYG is the incremental difference in evLY between the intervention and the comparator arms.

E4. Sensitivity Analyses

To demonstrate effects of uncertainty on both costs and health outcomes, we conducted numerous sensitivity analyses. We varied input parameters using available measures of parameter uncertainty (i.e., standard errors where available) or reasonable ranges to evaluate the sensitivity of the findings. We conducted one-way sensitivity analyses to identify the impact of parameter uncertainty and key drivers of model outcomes. Probabilistic sensitivity analyses were also performed by jointly varying all model parameters over 1,000 simulations, then calculating 95% credible range estimates for each model outcome based on the results.

Table E20. Tornado Diagram Inputs and Results, Health Care System Perspective

Input Name	Lower Input ICER	Upper Input ICER	Lower Input	Upper Input
HR on MCI to Mild Transition	$633,000	Dominated	These values are based on a confidential input. We varied this input across a range that included values above and below 1 and 0.31 units wide.	
Adjustment to MCI Hazard Ratio to Calculate Mild Hazard Ratio	$1,954,000	$993,000	0.00	1.00
Percent of Moderate Alive Patients Moving to Severe	$1,421,000	$1,261,000	0.34	0.50
Patient Disutility Severe AD, LTC Setting	$1,255,000	$1,413,000	-0.71	-0.47
Relative Risk of Death from MCI	$1,259,000	$1,409,000	1.48	2.19
Patient Disutility MCI, Community Care Setting	$1,390,000	$1,273,000	-0.20	-0.14
Probability of Symptomatic ARIA, Discontinue Due to AE	$1,387,000	$1,271,000	0.08	0.12
Percent of Mild Alive Patients Moving to Moderate	$1,391,000	$1,287,000	0.28	0.42
Patient Disutility Moderate AD, Community Care Setting	$1,302,000	$1,357,000	-0.43	-0.29
Percent of MCI Alive Patients Moving to Mild	$1,371,000	$1,317,000	0.19	0.28

AD: Alzheimer's disease, AE: adverse event, ARIA: amyloid-related imaging abnormalities, HR: hazard ratio, ICER: incremental cost-effectiveness ratio, LTC: long-term care, MCI: mild cognitive impairment

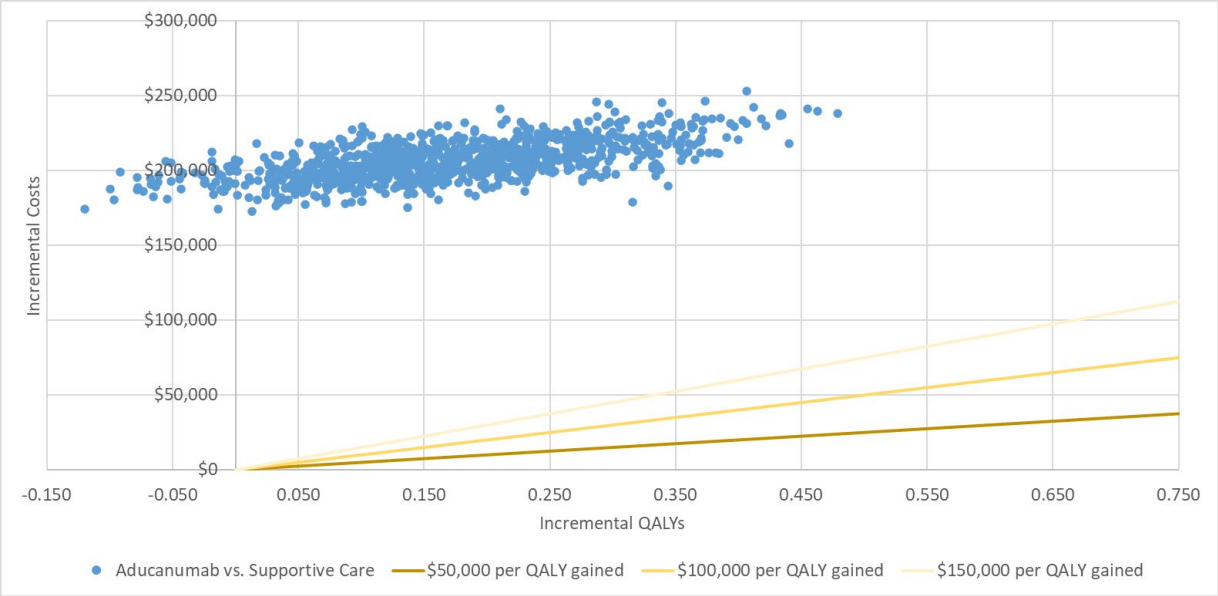
Table E21. Results of Probabilistic Sensitivity Analysis for Aducanumab versus Supportive Care

Health Care System Perspective	Aducanumab		Supportive Care		Incremental	
	Mean	Credible Range*	Mean	Credible Range	Mean	Credible Range
Total Costs	$548,000	$489,000-$609,000	$341,000	$295,000-$396,000	$206,000	$182,000-$233,000
Total QALYs	3.49	3.16-3.82	3.32	3.03-3.59	0.17	-0.03-0.37
Societal Perspective	Aducanumab		Supportive Care		Incremental	
	Mean	Credible Range*	Mean	Credible Range	Mean	Credible Range
Total Costs	$841,000	$758,000-$930,000	$637,000	$558,000-$723,000	$204,000	$180,000-$229,000
Total QALYs	3.12	2.78-3.46	2.94	2.68-3.22	0.17	-0.03-0.38

QALY: quality-adjusted life year

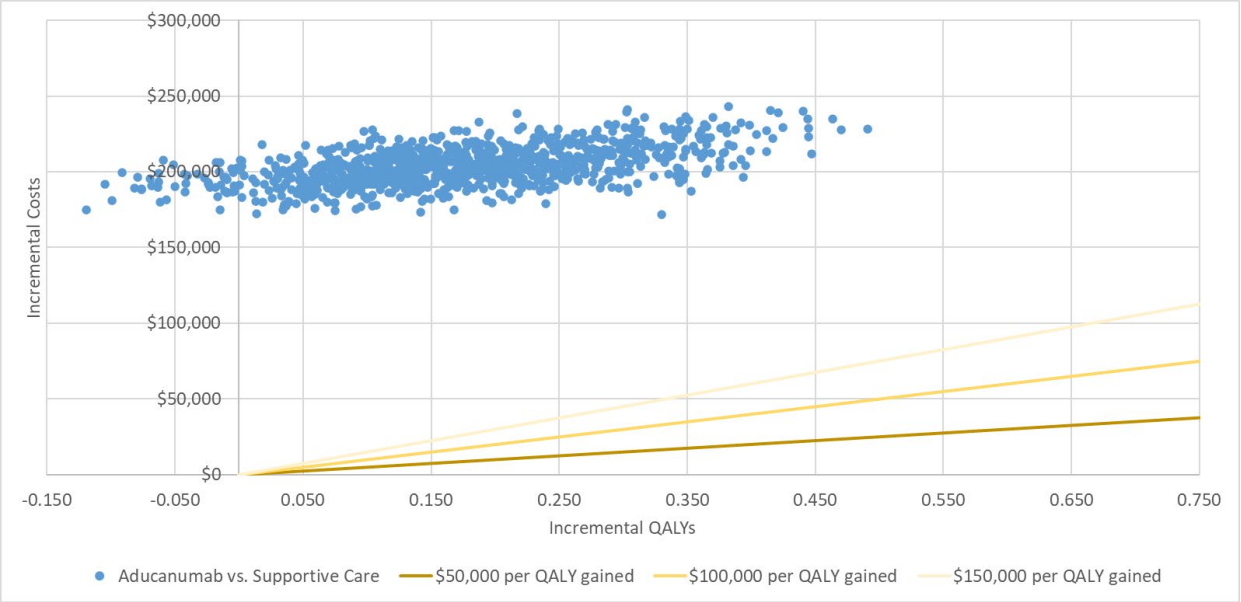
*Credible range calculated at 2.5 and 97.5 percentiles.

Figure E1. Probabilistic Sensitivity Analysis Results: Cost-Effectiveness Clouds, Health Care System Perspective



QALY: quality-adjusted life year

Figure E2. Probabilistic Sensitivity Analysis Results: Cost-Effectiveness Clouds, Societal Perspective



QALY: quality-adjusted life year

E5. Scenario Analyses

Table E22 presents the results from a scenario analysis that assumed treatment stopped once a patient reached moderate AD. In our base-case analysis, we assumed aducanumab treatment stopped at severe AD. In this scenario, even though aducanumab treatment stops once a patient reaches moderate AD, we do not model any catch-up period during the moderate AD health state. In other words, the hazard ratio for transitions out of moderate AD still equates to 1.0 as it did in the base case with the patient on aducanumab treatment. All other base-case inputs remained the same.

Table E22. Incremental Results from Scenario Analysis Assuming Treatment Stop at Moderate AD

Health Care System Perspective					
Treatment	**Comparator**	**Cost per QALY Gained**	**Cost per evLYG**	**Cost per Life Year Gained**	**Cost per Additional Year in the Community**
Aducanumab	Supportive care	$952,000	$729,000	$1,020,000	$911,000
Modified Societal Perspective					
Treatment	**Comparator**	**Cost per QALY Gained**	**Cost per evLYG**	**Cost per Life Year Gained**	**Cost per Additional Year in the Community**
Aducanumab	Supportive care	$908,000	$668,000	$1,010,000	$897,000

AD: Alzheimer's disease, evLYG: equal value of life years gained, QALY: quality-adjusted life year

E6. Model Validation

Model validation followed standard practices in the field. First, we provided preliminary model structure, methods and assumptions to manufacturers, patient groups, and clinical experts. Based on feedback from these groups, we refined data inputs used in the model, as needed. Second, we tested all mathematical functions in the model to ensure they were consistent with the report (and supplemental materials). We also conducted sensitivity analyses with null input values to ensure the model was producing findings consistent with expectations. Further, as part of ICER's efforts in acknowledging modeling transparency, we shared the model with Biogen for external verification shortly after publishing the draft report for this review.

Model validation was also conducted in terms of comparisons to other model findings. We searched the literature to identify models that were similar to our analysis, with comparable populations, settings, perspective, and treatments.

Prior Economic Models

To our knowledge, this is the first economic evaluation of aducanumab. There have been prior economic evaluations for AD treatments that were for non-disease-modifying treatments and there have been prior economic evaluations for hypothetical disease-modifying treatments. Our model structure was similar to the model structure presented by Neumann and colleagues[32] that evaluated the cost effectiveness of donepezil, a non-disease-modifying treatment for AD. Quality-of-life inputs and the inclusion of caregiver impact were also similar. This same model structure has been implemented widely across the disease area. Unlike the Neumann and colleagues' paper, our model structure also included an MCI health state due to the expected use and indication for aducanumab to start earlier on in the disease. Similar to the study by Neumann and colleagues, our analysis suggested there were benefits of treatment associated with the delay to more severe stages. The study by Neumann and colleagues presented estimates from both the health care system and societal perspective.[32] Similar to our findings, their incremental cost-effectiveness ratio from the societal perspective was more favorable than their incremental cost-effectiveness ratio from the health care system perspective. From our base-case analysis, the societal perspective incremental cost-effectiveness ratio was 5% less than the incremental cost-effectiveness ratio from the health care system perspective. The spread between perspectives from the study by Neumann and colleagues was slightly larger; their incremental cost-effectiveness ratio from the societal perspective was 15% less than their incremental cost-effectiveness ratio from the health care system perspective. This is largely driven by the assumed treatment effectiveness. When we update the assumptions in our model to assume a similar treatment effectiveness as what was assumed in the study by Neumann and colleagues, the spread we calculate between perspectives (30%) becomes larger than what was reported in their study.

A recent study by Green and colleagues[31] conducted a cost-effectiveness analysis of a hypothetical disease-modifying treatment for AD. This hypothetical model also started their model in the MCI due to AD health state to capture the earlier treatment initiation expected of potential disease-modifying treatments. For this hypothetical treatment, an annual cost of $5,000 was assumed and the treatment was assumed to be associated with a 20% risk reduction in disease progression. Their base-case cost-effectiveness estimate was approximately $50,000. When we use our model and update the annual cost of aducanumab to $5,000 and assign a 20% reduction in disease progression for aducanumab, the resulting incremental cost-effectiveness ratio is approximately $80,000. Differences in other population characteristics and other model inputs, exist, but this exercise shows how the model behaves similarly when two key drivers (e.g., treatment effectiveness and treatment cost) are the same. Similar to our analysis, they report expected gains in life years and time in less severe health AD health states.

F. Potential Budget Impact: Supplemental Information

F1. Methods

We used results from the same model employed for the cost-effectiveness analyses to estimate total potential budget impact. Potential budget impact was defined as the total differential cost of using each new therapy rather than relevant existing therapy for the treated population, calculated as differential health care costs (including drug costs) minus any offsets in these costs from averted health care events (assuming the health care system perspective). We provide supporting findings of the potential budget impact assuming the modified societal perspective given that this perspective was included as a co-base-case in the cost-effectiveness analysis. All costs were undiscounted and estimated over one- and five-year time horizons. The five-year timeframe was of primary interest, given the potential for cost offsets to accrue over time and to allow a more realistic impact on the number of patients treated with the new therapy.

The potential budget impact analysis included the MCI due to AD and mild AD populations eligible for treatment with aducanumab. To estimate the size of the potential candidate populations for treatment, we used a similar approach to that employed by Potashman and colleagues in estimating the prevalence in Europe of MCI due to AD and mild AD with confirmed beta-amyloid pathology.[7] This "funnel-based" approach used estimates of the prevalence of MCI and mild AD in the US, the proportion of those patients presenting to health care professionals for diagnosis, the proportion diagnosed, and the proportion confirmed to be positive for beta-amyloid following testing. An unpublished analysis has used this approach to derive an estimate of 1.4 million patients in the US eligible for AD treatment that targets beta-amyloid, based on 2019 data. We assumed that 20% of these patients would initiate treatment in each of the five years, or approximately 280,000 patients per year.

ICER's methods for estimating potential budget impact are described in detail elsewhere and have recently been updated.[98,99] The intent of our revised approach to budgetary impact is to document the percentage of patients that could be treated at selected prices without crossing a budget impact threshold that is aligned with overall growth in the US economy.

Briefly, we evaluate a new drug that would take market share from one or more drugs and calculate the blended budget impact associated with displacing use of existing therapies with the new intervention. In this analysis, we assumed that aducanumab will be added on to standard care for these patients. That is, the analysis assumed that no current treatments are likely to be displaced by use of the new treatment within the eligible population.

Using this approach to estimate potential budget impact, we then compared our estimates to an updated budget impact threshold that represents a potential trigger for policy mechanisms to improve affordability, such as changes to pricing, payment, or patient eligibility. As described in ICER's methods presentation (https://icer.org/our-approach/methods-process/value-assessment-framework/topic-selection/), this threshold is based on an underlying assumption that health care costs should not grow much faster than growth in the overall national economy. From this foundational assumption, our potential budget impact threshold is derived using an estimate of growth in US gross domestic product (GDP) +1%, the average number of new drug approvals by the FDA over the most recent two-year period, and the contribution of spending on retail and facility-based drugs to total health care spending.

For 2019-2020, therefore, the five-year annualized potential budget impact threshold that should trigger policy actions to manage access and affordability is calculated to total approximately $819 million per year for new drugs.

F2. Results

Health Care System Perspective Results

Table F.1 illustrates the per-patient five-year average annual total health system costs by treatment and the average net annual cost calculations in more detail, based on the annual price ($56,000 per year), and the prices to reach $150,000, $100,000, and $50,000 per QALY for aducanumab compared to standard of care.

Table F1. Per-Patient Average Annual Total and Average Annual Net Costs Over a Five-Year Time Horizon (Health Care System Perspective)

	Average Annual Per Patient Total and Net Costs*			
	Annual Price ($56,000 per Year)	**$150,000/QALY**	**$100,000/QALY**	**$50,000/QALY**
Aducanumab (Total)	$78,590	$46,460	$45,100	$43,730
Standard of Care (Total)	$43,350	$43,350	$43,350	$43,350
Difference (Net)	$35,240	$3,110	$1,750	$380

QALY: quality-adjusted life year

*Average annual total and net costs differ from the average budget impact given the assumed initiation of treatment of 20% per year that gives the budget impact findings more weight to earlier yearly costs (first- and second-year costs) vs. later yearly costs (fourth- and fifth-year costs). The averages presented in this table are simple averages over years one through five.

Modified Societal Perspective Results

Table F2. illustrates the per-patient five-year average annual total health system costs by treatment and the average net annual cost calculations in more detail, based on the annual price ($56,000 per year), and the prices to reach $150,000, $100,000, and $50,000 per QALY for aducanumab compared to standard of care, assuming the modified societal perspective.

Table F2. Per-Patient Average Annual Total and Average Annual Net Costs Over a Five-Year Time Horizon (Modified Societal Perspective)

	Average Annual Per Patient Total and Net Costs*			
	Annual Price ($56,000 per Year)	**$150,000/QALY**	**$100,000/QALY**	**$50,000/QALY**
Aducanumab (Total)	$120,740	$89,140	$87,740	$86,330
Standard of Care (Total)	$86,570	$86,570	$86,570	$86,570
Difference (Net)	$34,170	$2,580	$1,170	-$230

QALY: quality-adjusted life year

*Average annual total and net costs differ from the average budget impact given the assumed initiation of treatment of 20% per year that gives the budget impact findings more weight to earlier yearly costs (first- and second-year costs) vs. later yearly costs (fourth- and fifth-year costs). The averages presented in this table are simple averages over years one through five. For example, the negative net costs for the $50,000/QALY finding presented in this table are not consistent with the increased costs found for the estimated budget impact over five years.

G. Public Comments

This section includes summaries of the public comments prepared for the virtual CTAF public meeting on Thursday, July 15, 2021. These summaries were prepared by those who delivered the public comments at the meeting and are presented in order of delivery.

A video recording of all comments can be found here. Conflict of interest disclosures are included at the bottom of each statement for each speaker who is not employed by a pharmaceutical manufacturer.

Maha Radhakrishnan, MD
Chief Medical Officer
Biogen

The FDA has approved ADUHELM under the accelerated approval pathway based on reduction in amyloid plaques, a biomarker that is reasonably likely to predict clinical benefit. ADUHELM has been studied extensively in clinical trials, and we refer you to the data as set out in the USPI, the US label, which outlines the results of the studies.

As the indication statement in the USPI sets out: ADUHELM is an amyloid beta-directed antibody indicated for the treatment of Alzheimer's disease. Treatment with ADUHELM should be initiated in patients with mild cognitive impairment or mild dementia stage of disease, the population in which treatment was initiated in clinical trials. There are no safety or effectiveness data on initiating treatment at earlier or later stages of the disease than were studied. This indication is approved under accelerated approval based on reduction in amyloid-beta plaques observed in patients treated with ADUHELM. Continued approval for this indication may be contingent upon verification of clinical benefit in confirmatory trial(s).

Assessing the first treatment for Alzheimer's disease is a complex matter that requires innovative thinking and new methodological framework. We regret that the ICER assessment missed the mark on this. The central problem surrounding this assessment is that it applies a surprisingly narrow framework to the burden of AD and the value of AD treatments. The report discounts the possible holistic value of ADUHELM and does not accurately reflect the potential effect of treating older adults with MCI due to AD or mild AD with a drug that removes amyloid plaques. Many AD patients and caregivers looking into a future after an AD diagnosis are terrified. Many suffer from depression, anxiety, and agitation as they cope with this new reality. This is not just limited to a small group of individuals but magnified as patients have an average of three caregivers. And caregivers and their families certainly struggle with AD's psychological and physical impact. They witness it destroy their loved ones but feel helpless and alone. There is no cure for Alzheimer's disease, and until ADUHELM's approval, there was no drug approved since 2003. At Biogen, we

have been researching a treatment for Alzheimer's for more than a decade, learning from setbacks, following the science, and persisting in our commitment to the community.

And yet, this report undervalues AD's burden and this moment in history. There is a reason why of a total of eleven public comments on this report - the universal theme was that this analysis underestimates treatment value to patients and their caregivers. Every public comment has highlighted that ICER's assessment can't regard the challenges of AD in the same way as other diseases – namely – it can't value ADUHELM with the same measures for less severe diseases.

It is inappropriate to blend trials with different characteristics. The assessment wrongly assumes patients had the same exposure to high-dose treatment between trials. This makes the base case fundamentally flawed and undervalues AD treatments for patients and caregivers.

Models are based on assumptions. ICER's model makes a number of pessimistic assumptions – for example – the report assumes that patients remain on therapy beyond the time period in which the physician would deem it appropriate to continue to treat. These ultimately underestimate the value of a treatment option to Alzheimer's disease patients and caregivers.

The report's price threshold is inappropriate for the severity of the disease. The assessment uses price thresholds applied to other diseases that are too low to capture value in Alzheimer's disease – and again – what this means is that it undervalues AD treatments for patients and caregivers.

In my lifetime, it is a privilege to be part of this moment here and now where I can tell my family members, friends, and this community that there is a new treatment option that we believe is likely to spur development in future AD medicines. While we launch Aduhelm, we are also continuing to invest in more than 30 clinical development programs. These include several potential additional treatments for Alzheimer's disease and other debilitating neurological conditions such as Parkinson's disease, amyotrophic lateral sclerosis (ALS), and stroke. Today AD is a progressive disease, but as the field continue to innovate, our hope is that one day it will be different.

Pam Montana
Patient with AD

- ***No conflicts of interest to disclose.***

Thank you for the opportunity to speak with you. My name is Pam Montana and I am currently living with early onset, early stage [AD]. I was diagnosed in 2016 and have embraced my diagnosis by participating in clinical trials, using my voice to help find a cure, raising money and advocating for research and to remove the stigma of AD. I am doing well and earlier this week my neurologist agreed that indeed, I am doing well, and I am stable. My progression has been slow and for that I am grateful.

For years leading up to this moment, I have spoken to many audiences about my hope for an Alzheimer's treatment that could help future generations, and potentially even help me... I've spoken about hope and how important such a drug would be for me. I have spoken about my children and my grandchildren and my husband, and how important more time with them is. My message has been this: I need more time! And now, maybe, this just might be possible.

If my doctors at UCSF [University of California, San Francisco] agree that I am a good candidate for an Alzheimer's treatment, I will gladly take it. Even if it were to be a huge commitment, for me it would be worth it.

All drugs have side effects, but I trust UCSF and I trust my neurologist. If together we decide a treatment is worth the risk, I would hope that the availability, the cost, and the insurance coverage would allow me to pursue a potentially life-changing option.

I know the newest treatment won't cure my Alzheimer's but it will give me more time and that is what I want and what I value. More time to enjoy my family and to use my voice to raise awareness about Alzheimer's. I want more time to travel, to spend time with my friends, to achieve my life goals.

After my diagnosis, the hardest, most difficult discussion I had was with my oldest grandson. He asked me if I would remember him when my disease progressed. I told him that I would never forget him, but that I might not know his name.

A treatment could give me the chance to remember his name, for more days, more weeks, more months. This would matter to me. As you make your decisions, please keep this, all the others living with Alzheimer's desires for more time, in your mind.

Thank you.

Laura Jones
Caregiver and Advocate

- ***No conflicts of interest to disclose.***

I had many thoughts about why the ICER score may not be accurate as well as thoughts on how to manage the rollout of this drug.

The negative effect on diversity bothered me mostly because the drug has nothing to do with that. It is because of our country's faulty delivery system for medical care. I am upset they used that against the drug. The scope of use is extremely limited making a diversity calculation impossible.

My main concern on the rollout is (to be honest) how to convince caregivers not to lie to try to get the drug. I believe I, as a past caregiver, can personally help with that.

My most personal concern is about the fact that if MCI and mild AD are the only stages appropriate, those under 65 may have a problem getting it.

My husband for instance was diagnosed in 2006. He lost his job (and insurance) in 2007. We were granted SSDI [Social Security Disability Insurance] in 2010, but only got Medicare two years later. He would have been in the eligible AD stage for the drug before he got on Medicare. No way would we have been able to pay for it. We went years with no insurance because I could not pay for it.

Younger onset people, whom I believe will be most likely to tolerate it, will have a very hard time getting it.

I care very much about this issue and believe I have an overall understanding of all sides to be appropriately objective.

Matthew Baumgart
Vice President of Health Policy
Alzheimer's Association

- ***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.***

The Alzheimer's Association is the leading voluntary health organization in Alzheimer's care, support, and research. We are the world's largest non-profit funder of Alzheimer's research and are committed to funding efforts by scientists around the world to find preventions, treatments, and ultimately, a cure for AD – to bring much needed relief to millions of American families.

As a science-based organization, we undertook a thorough review of the evidence and clinical trial data on aducanumab and consulted with numerous scientific experts. We heard some differing views. But in the end, we concluded that while it is not a cure and not the best treatment that will ever be available, Aduhelm does offer as many as several years of positive benefits – benefits for a devastating, heartbreaking, burdensome, and fatal disease for which there is no alternative. The FDA made the right decision to conditionally approve Aduhelm.

And now that we have an FDA-approved treatment, we must turn our attention to ensuring all those who could potentially benefit from the drug have access to it. We must eliminate all barriers to access – at every stage of the process, throughout the patient journey. Access means individuals must have the ability to get diagnosed and to see an appropriate specialist. Access means the ability to get to PET and infusion facilities. Access means a drug price that is not unacceptably high – and the price set by Biogen is unacceptably high. And, access means payers must cover the drug. It is this latter point that ICER's report threatens. Some payers have already cited ICER's report as an excuse not to cover the drug.

This will continue to happen because the report does not assess the full and true value of Aduhelm.

A true value assessment must take into account what is truly of value to patients and caregivers. For patients, it is maintaining their independence and their identity – extending their ability to live their lives on a day-to-day basis. For caregivers, it means reducing distress and burden and increasing their ability to achieve their goals in life. To both patients and caregivers, the value of this drug is being able to spend more time together as a family. In addition, Aduhelm fills a huge unmet need, which is of tremendous value to those with the disease and their caregivers. They have no other alternatives. Having one – finally, one – even one that falls short of perfect, adds value.

Having an alternative to nothing adds value in another way: it is a spark for innovation and the gateway to additional and better therapies. In response to public comments, ICER argues that approval of Aduhelm will stifle research on non-beta amyloid therapies and therefore hinder innovation. We categorically reject this ahistorical assertion. Whether it is therapies for LDL cholesterol, or treatments for HIV/AIDS, or even the symptomatic treatments for Alzheimer's – history repeatedly shows the first approved therapy spurs research and development in a variety of avenues and pathways that lead to the second and third and fourth therapies, each improving on the earlier treatments.

Let me raise just one additional item of important social value in the case of Alzheimer's. Even without a disease-modifying therapy, the benefits of an early diagnosis of Alzheimer's are well-documented and well-known, including lower health and long-term care costs. Unfortunately, too many individuals with Alzheimer's are diagnosed too late – if they are diagnosed at all. And the problem is even more acute among underserved communities. 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 said they sometimes choose not to even assess an individual's cognition because, if the individual is eventually diagnosed, treatment options are limited. The value of a treatment is that many in the health care system will finally recognize the value of a diagnosis. Aduhelm will help drive earlier diagnosis, which has numerous personal, social, and economic benefits – even if the direct effect of the drug is limited.

It is a shame that the ICER report does not fully take into account the value of Aduhelm, and it is unfortunate that this report will be used in efforts to deny access to this drug for those who could benefit.

Russ Paulsen
Chief Operating Officer
Us Against Alzheimer's

- ***Us Against Alzheimer's receives financial support from Biogen, Eisai, and their competitors. Russ Paulsen has also received payments for services such as consulting fees or honoraria in excess of $5,000.***

UsAgainstAlzheimer's is a patient- and caregiver-driven, nonprofit organization that exists to conquer Alzheimer's disease. UsAgainstAlzheimer's presses for greater urgency in the quest to end Alzheimer's disease and related dementias—and we seek to ensure that the voices of those living with this awful disease are heard.

We appreciate the ICER research team's engagement with UsAgainstAlzheimer's and the Alzheimer's community and considering the experiences of those living with AD—specifically, acknowledging and incorporating the quality of life, health, and productivity of the caregiver in its base case analyses.

We're also pleased that ICER considered the findings of our What Matters Most and caregiver burden research. These are huge steps forward in the economic model and we applaud the ICER team for that work.

We appreciate the report's acknowledgement of the limitations of the available published sources of data for inclusion into the economic model. But, we must not paper over those limitations. Here are three of concern:

1. Costs that increase as Alzheimer's progresses have significant limitations that could impact the overall results. For example, healthcare costs by disease stage were based on a study conducted in 1 US county (Olmstead County, MN) that is not nationally representative and also did not include all healthcare costs.

2. Caregiver quality of life is estimated from a study conducted over 20 years ago with known methodological limitations to detect change as AD progresses. The use of this study—even after adjustments—provoked comments from many reviewers of the Draft Evidence Report because—for anyone who has been a caregiver for an Alzheimer's patient as they progress—it simply lacks face validity.

3. The model assumes only one caregiver per patient, which goes against we know about the ratio of caregivers to patients.

If you review the comments on the Draft Evidence Report, you'll see there are other gaps.

To be clear, this isn't the fault of Dr. Whittington or her team. Published research on these inputs was not available. That said, we expected to see more in the report to account for or note these missing or underestimated inputs and impacts they could have had on the results of the model. Sensitivity analyses were relatively limited given the number of uncertainties in the inputs.

In light of all of that, it's surprising that ICER's report estimates a value of aducanumab down to the tens of dollars. That level of precision, given all of the unknows, is like measuring the volume of a swimming pool by how many five-gallon buckets of water went in. Only this isn't about how big a pool is – this is about people's lives.

Because, the alternative to aducanumab is a relentless decline into the most feared disease among older Americans. It's people becoming totally dependent. And then dying.

We shouldn't let that happen in America when there's an approved therapy.

Until better source data is available, the findings from this model should be considered interim—as informative but not definitive. ICER should commit to an annual update of this evidence report, adding in newly available data to improve the accuracy of the results.

It's incumbent upon all of us—including ICER-- to conduct research to address knowledge gaps identified in this report. UsAgainstAlzheimer's has already called on Biogen to complete their Phase IV trial faster than the original plan, and with a diverse population. We also believe now is the time for careful, comprehensive collection of real-world evidence.

Regarding the idea of uncertainty around efficacy—patients know this isn't a silver bullet—it's not penicillin. But the alternative is a miserable death. We shouldn't treat Alzheimer's patients as second-class citizens, where the accelerated approval pathway is for other people, not for them. Thousands and thousands of lives have been saved in, for example, lung cancer, thanks to accelerated approval. Alzheimer's patients should get the same benefit of the doubt.

Finally, as we recognized the uncertainty in ICER's the data, we encourage ICER's leadership to not overstate the findings in this report. "We rate the evidence to be insufficient" is a far cry from "the FDA…has failed in its responsibility to protect patients and families from unproven treatments with known harms."

Thank you.

Brian Callaghan, MD, MS, FAAN
American Academy of Neurology

- ***No conflicts of interest to disclose.***

The American Academy of Neurology (AAN) is the world's largest neurology specialty society representing more than 36,000 neurologists and clinical neuroscience professionals. Its members have specialized training in diagnosing, treating, and managing disorders of the brain and nervous system, including mild cognitive impairment and Alzheimer's disease.

AAN members are dedicated to promoting the highest quality patient-centered neurologic care by providing safe and effective treatments but are unsure if aducanumab is the best option for their patients based on the current data. The AAN has been monitoring aducanumab's approval process and is concerned about implications relating to several considerations highlighted in the Institute for Clinical and Economic Review's (ICER) report including drug efficacy and costs to the health care system and patients.

The AAN appreciates many of the considerations included in the ICER report related to the ENGAGE and EMERGE clinical trials. The highly irregular clinical trial process leaves a plethora of questions about the efficacy patients and providers can expect from aducanumab as it begins to see widespread use. Many AAN members now face pressure for appropriate prescribing, given the uncertainties surrounding efficacy. The AAN also echoes ICER's concerns regarding the lack of racial and ethnic diversity in the clinical trial population, given the disproportionate impact of Alzheimer's disease on Black and Hispanic individuals. Given the current data, future clinical trials are needed to firmly establish or refute efficacy of aducanumab and to see if results are generalizable to other populations.

The AAN was heartened to see the FDA update the label to patients with mild cognitive impairment or mild dementia, as this is in line with the recommendations, we sent to the FDA prior to aducanumab's approval. However as noted in ICER's revised evidence report, Biogen has set an annual price for aducanumab at $56,000. Unfortunately, patients are likely to bear a significant amount of financial hardship given the rising out-of-pocket costs of many neurologic medications that has occurred over the last several years. Furthermore, the impact on Medicare Part B spending cannot be overstated as aducanumab could cost more than a trillion dollars before its clinical benefit is adequately demonstrated, depending on how many patients take the drug. The AAN agrees with ICER that due to the high systemic and out-of-pocket costs, aducanumab could only be administered to a very small number of patients before the need for federal policy changes to address access and affordability. The budget impact on the health care system and individual patients is very concerning, including factors not included in the ICER analysis such as ancillary costs associated with infusions and testing.

The AAN is grateful to ICER for conducting this thorough review of a drug that will have such an impact on neurologic patients and our health system broadly. We hope this report continues to inform stakeholder discussions on critical questions for aducanumab including the required Phase IV clinical trial and insurance coverage.

H. Conflict of Interest Disclosures

Tables H1 through H3 contain conflict of interest (COI) disclosures for all participants at the virtual CTAF public meeting on Thursday, July 15, 2021.

Table H1. CTAF Member Participants

Ralph G. Brindis, MD, MPH, MACC, FSCAI, FAHA,* Clinical Professor of Medicine, UCSF	**Sei Lee, MD,*** Associate Professor of Medicine, Division of Geriatrics, UCSF
Felicia Cohn, PhD,* Bioethics Director, Kaiser Permanente, Orange County; Clinical Professor of Bioethics, Department of Medicine, University of California, Irvine School of Medicine	**Elizabeth J. Murphy, MD, DPhil,*** Professor of Clinical Medicine, UCSF; Chief, Division of Endocrinology and Metabolism, Zuckerberg San Francisco General Hospital
Sanket Dhruva, MD, MHS, FACC,* Assistant Professor of Medicine, UCSF	**Kathryn A. Phillips, PhD,*** Professor of Health Economics and Health Services Research; Director and Founder, UCSF Center for Translational and Policy Research on Personalized Medicine; Department of Clinical Pharmacy/School of Pharmacy, UCSF Institute for Health Policy Studies, and UCSF Comprehensive Cancer Center
Rena K. Fox, MD,* (Chair) Professor of Medicine, UCSF	**Ann Raldow, MD, MPH,*** Assistant Professor, Department of Radiation Oncology, UCLA David Geffen School of Medicine
Bob Collyar,* Patient Advocate in Research	**Richard Seiden, JD,*** Patient Advocate, Retired Partner, Foley & Lardner LLP
Jeffrey Hoch, PhD,* Associate Director, Center for Healthcare Policy and Research, UC Davis	**Joanna Smith, LCSW, MPH, CHA,*** Chief Executive Officer, Healthcare Liaison, Inc.
Jeffrey Klingman, MD,* Chief of Neurology, Kaiser Permanente, Walnut Creek	**Anthony Sowry,*** Patient Advocate and Lead Volunteer, California, National Patient Advocate Foundation; Senior Vice President, Maritime Container Shipping (Retired)
Annette Langer-Gould, MD, PhD,* Regional Lead for Clinical/Translational Neuroscience, Southern California Permanente Medical Group, Kaiser Permanente; MS Specialist, LA Medical Center	

*No conflicts of interest to disclose, defined as individual health care stock ownership (including anyone in the member's household) in any company with a product under study, including comparators, at the meeting in excess of $10,000 during the previous year, or any health care consultancy income from the manufacturer of the product or comparators being evaluated.

Table H2. Policy Roundtable Participants and COI Disclosures

Policy Roundtable Participant	Conflicts of Interest
Matthew Baumgart, Vice President of Health Policy, Alzheimer's Association	The 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.
Leslie Fish, RPh, PharmD, Vice President of Clinical Pharmacy, IPD Analytics	Leslie Fish is an employee of IPD Analytics.
Patrick Gleason, PharmD, Assistant Vice President, Health Outcomes, Prime Therapeutics	Patrick Gleason is an employee of Prime Therapeutics.
Victor W. Henderson, MD, MS, Professor, Epidemiology and Population Health and Neurology and Neurological Sciences; Director, Alzheimer's Disease Research Center, Stanford University	No conflicts of interest to disclose.
Laura Jones, Caregiver and Advocate	No conflicts of interest to disclose.
Sarah Kremen, MD, Director, Neurobehavior Program, Jona Goldrich Center for Alzheimer's and Memory Disorders, Cedars-Sinai Medical Center	Sarah Kremen served as a site PI for aducanumab trials PRIME and ENGAGE.
Chris Leibman, PharmD, MS, Head of Value and Access, Biogen	Chris Leibman is an employee of Biogen.
Mark McClellan, MD, PhD, Director, Duke University Margolis Center for Health Policy	Receipt of monetary value, including salary and other payments for services. Equity interests in individual stocks, stock options, or other ownership interests in excess of $10,000. Status as an officer, board member, trustee, owner, or employee of a health care company, or an organization that receives more than 25% of its funding from health care companies.

Table H3. ICER Staff and Consultants

Jonathan D. Campbell, PhD, MS,* Senior Vice President for Health Economics, ICER	**Steven D. Pearson, MD, MSc,*** President, ICER
Laura Cianciolo,* Program Manager, ICER	**David M. Rind, MD, MSc,*** Chief Medical Officer, ICER
Noemi Fluetsch, MSc, MPH,* Research Assistant, Health Economics and Outcomes Research, ICER	**Patricia G. Synnott, MS, MALD,*** Senior Manager, CEA Registry and Global Health Initiatives, Center for the Evaluation of Value and Risk in Health
Grace A. Lin, MD,* Associate Professor of Medicine and Health Policy, UCSF	**Azanta Thakur,*** Program and Event Coordinator, ICER
Avery McKenna,* Research Assistant III, Evidence Synthesis, ICER	**Melanie D. Whittington, PhD, MS,*** Associate Director of Health Economics, ICER
Emily Nhan,* Research Assistant, ICER	

*No conflicts of interest to disclose, defined as individual health care stock ownership (including anyone in the member's household) in any company with a product under study, including comparators, at the meeting in excess of $10,000 during the previous year, or any health care consultancy income from the manufacturer of the product or comparators being evaluated.