Lecanemab for Early Alzheimer's Disease

Evidence Report

March 1, 2023

Prepared for

AUTHORS:

Grace Lin, MD
Medical Director for Health Technology Assessment
Institute for Clinical and Economic Review

Melanie D. Whittington, PhD, MS
Director of Health Economics
Institute for Clinical and Economic Review

Abigail Wright, PhD, MSc
Senior Research Lead, Evidence Synthesis
Institute for Clinical and Economic Review

Foluso Agboola, MBBS, MPH
Vice President of Research
Institute for Clinical and Economic Review

Serina Herron-Smith, BA
Associate Research Manager
Institute for Clinical and Economic Review

Steven D. Pearson, MD, MSc
President
Institute for Clinical and Economic Review

David Rind, MD, MSc
Chief Medical Officer
Institute for Clinical and Economic Review

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Grace Lin served as the lead author for the report. Abigail Wright led the systematic review in collaboration with Serina Herron-Smith. Foluso Agboola provided methodologic guidance. Melanie Whittington developed the economic model. David M. Rind and Steven D. Pearson provided methodologic guidance on the clinical and economic evaluations. We would also like to thank Noemi Fluetsch, Monica Frederick, Kelsey Gosselin, and Yasmine Kayali for their contributions to this report. Additionally, we would like to thank UsAgainstAlzheimer's for connecting us with individuals living with Alzheimer's disease and caregivers to help us better understand their lived experiences.

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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 25% 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. No life science companies relevant to this review currently participate in this program. For a complete list of funders and for more information on ICER's support, please visit https://icer.org/who-we-are/independent-funding/.

For drug topics, in addition to receiving recommendations from the public, ICER scans publicly available information and also benefits from a collaboration with IPD Analytics, an independent organization that performs analyses of the emerging drug pipeline for a diverse group of industry stakeholders, including payers, pharmaceutical manufacturers, providers, and wholesalers. IPD provides a tailored report on the drug pipeline on a courtesy basis to ICER but does not prioritize topics for specific ICER assessments.

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The findings contained within this report are current as of the date of publication. Readers should be aware that new evidence may emerge following the publication of this report that could potentially influence the results. ICER may revisit its analyses in a formal update to this report in the future.

The economic models used in ICER reports are intended to compare the clinical outcomes, expected costs, and cost-effectiveness of different care pathways for broad groups of patients. Model results therefore represent average findings across patients and should not be presumed to represent the clinical or cost outcomes for any specific patient. In addition, data inputs to ICER models often come from clinical trials; patients in these trials may differ in real-world practice settings.

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: https://icer.org/assessment/alzheimers-disease-2022/#overview

Expert Reviewers

VICTOR HENDERSON, MD, MS
Professor
Stanford University
No relevant conflicts of interest to disclose, defined as more than $10,000 in healthcare company stock or more than $5,000 in honoraria or consultancies during the previous year from health care manufacturers or insurers. Dr. Henderson has previously received honorarium for serving as an external reviewer on an ICER review in 2021.

JASON KARLAWISH, MD
Professor
University of Pennsylvania
Dr. Karlawish has served as a site investigator for clinical trials sponsored by Biogen, Eisai Co., Ltd and Eli Lilly & Co.

We also received comments from consultants of a patient organization but have not named them at their request. Those comments did result in some changes to the Report.

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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	Alzheimer's Disease Cooperative Study – Activities of Daily Living Inventory
AE	Adverse event
AHRQ	Agency for Healthcare Research and Quality
APOE ε4	Apolipoprotein ε4
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 more than 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 care for themselves. People living with AD require a substantial amount of caregiving, and eventually may require around-the-clock in-home or institutional care. Caregivers, most often unpaid family members and friends, 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, including 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 (DMTs) that slow or stop progression of the disease. Although aducanumab (Aduhelm™, Biogen) was granted accelerated approved for the treatment of AD in June 2021, there remain substantial uncertainties about its benefits and harms. In this report, we focus on lecanemab (Leqembi™, Eisai Co., Ltd), an anti-amyloid monoclonal antibody approved by the FDA on January 6, 2023, also under an accelerated pathway based on removal of amyloid plaques. A prior version of this report included a review of donanemab. Due to the manufacturer receiving a Complete Response Letter from the FDA on January 19, 2023 for donanemab's accelerated approval biologics license application, we have removed donanemab from the report.

Lecanemab was evaluated in a Phase III randomized clinical trial, CLARITY AD. The trial randomized 1,795 participants with early AD (i.e., mild cognitive impairment [MCI] or mild dementia due to AD) to a biweekly 10 mg/kg intravenous infusion or placebo. The primary clinical outcome was change in mean score on the Clinical Dementia Rating Scale – Sum of Boxes (CDR-SB). At 18 months, the lecanemab-treated group showed a statistically significant 27% slowing of cognitive decline compared with placebo, representing an average difference of about 0.5 points on the 18-point CDR-SB scale. Analyses of secondary endpoints, including other cognitive measures and patient and caregiver quality of life consistently favored the lecanemab-treated group. Among participants treated with lecanemab, 21.5% experienced amyloid related imaging abnormalities with edema/effusion (ARIA-E), ARIA-hemorrhage or superficial siderosis (ARIA-H), or both compared with 9.5% in the placebo group, and 3.5% of patients in the lecanemab group experienced symptomatic ARIA-E or -H compared with 0.2% in the placebo group.

We remain uncertain that amyloid removal is an appropriate surrogate outcome for clinical benefit and instead look to the clinical outcomes found in randomized trials. However, there is

disagreement among experts about the clinical meaningfulness of the magnitude of change in CDR-SB in the lecanemab trial.[7] We also remain concerned that real world ARIA occurrences and consequences may be more severe if, as expected, monitoring MRIs are not as frequent as in the clinical trial, the patient population treated differs from the trial population, and clinicians are less expert than those who participated in the randomized trial.

In aggregate, the net health benefits of **lecanemab** in patients with early AD may be small or even substantial, but there remains a possibility of net harm from ARIA. We rate treatment with lecanemab in MCI due to AD or mild AD as "Promising but Inconclusive" (**P/I**).

Table ES1. Evidence Ratings

Treatment	Comparator	Evidence Rating
Patients with Early Alzheimer's Disease		
Lecanemab	Supportive care only	P/I

We estimated the lifetime cost effectiveness of lecanemab in addition to supportive care as compared to supportive care alone from a health care sector 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). From both perspectives, lecanemab's annual price of $26,500 exceeded commonly used cost-effectiveness thresholds. ICER's Health Benefit Price Benchmark (HBPB) for lecanemab is $8,900 to $21,500, requiring a 66% to 19% discount from lecanemab's wholesale acquisition cost (WAC).

1. Background

ICER reviewed aducanumab for early Alzheimer's disease in 2021 (Aducanumab for Alzheimer's Disease: Effectiveness and Value[8]). Much of the background information in this evidence report is updated from that report with additional contextual information about lecanemab.

Alzheimer's disease (AD) is a fatal degenerative brain disease characterized by progressive loss of cognitive skills such as such as memory, language, navigation, and problem-solving, and physical function. It is the most common cause of dementia in the United States (US), accounting for up to 60-80% of all dementia diagnoses and is the sixth leading cause of death.[2] Direct costs of health care related to AD are estimated to be around $321 billion in 2022, and are projected to increase to just under $1 trillion in 2050.[2] However, the economic burden of the disease may be underestimated, as many non-medical costs such as home safety modifications, adult day care services, and adverse effects on caregiver health and productivity may not be included in cost estimates.[2]

AD affects an estimated 6.5 million Americans, or around 10% of the population aged 65 year or older, and around one-third of people aged 85 and older.[2] Early-onset AD, defined as the onset of AD prior to age 65, accounts for around 5% of cases and is associated with a larger genetic predisposition and differences in clinical and pathologic presentation.[9] Two-thirds of those diagnosed with AD are women,[2] and there is evidence that symptoms of the disease may manifest differently in women and men, particularly with respect to neuropsychiatric symptoms.[10,11] There are racial and ethnic differences in the incidence and prevalence of AD, with higher rates noted in the African American and Hispanic populations compared with non-Hispanic White and Asian populations.[2,12]

The hallmark of AD is the progressive accumulation of beta-amyloid protein plaques and neurofibrillary tangles of hyperphosphorylated tau protein in the brain;[1] these are hypothesized to lead to damage and eventual death of neurons over decades. Single-gene mutations that impact beta-amyloid formation (e.g., amyloid precursor protein and presenilin) are associated with early-onset AD. Genetic variants such as the apolipoprotein E (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.[13] Additionally, 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; however, the neuronal damage from accumulation of amyloid is thought to trigger a cascade leading to impairment in cognitive domains such as memory, language, executive function, and visuospatial function, which results in the loss of ability to perform instrumental and basic activities of daily living (e.g., paying bills, bathing, dressing, etc.).[14]

The course of AD can be described in three phases: preclinical disease, mild cognitive impairment (MCI) due to AD, and dementia due to AD. People living with AD begin to accumulate beta-amyloid in the brain in the preclinical phase up to 15 years prior to the onset of symptoms.[15] These changes can be detected through the cerebrospinal fluid (CSF) (e.g., decreased beta-amyloid and increased CSF tau protein levels) and imaging (e.g., amyloid on positron emission tomography [PET] scans). CSF and imaging biomarkers can be used to identify AD pathology as well as to guide therapy and to monitor the impact of therapeutic interventions.[16-18] Difficulty remembering recent conversations, names or events is often an early symptom, along with decreased awareness of financial scams[19]; depression and apathy may also be seen at this stage. The diagnosis of MCI is marked by a reduction in cognitive function; at this point, the patient can still live and function independently, although they typically show impairment in instrumental activities of daily living. Individuals 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, although other forms of dementia may be present as well.[20]. At this stage, a person typically needs a caregiver.

As the disease progresses, people living with AD become less and less independent and the need for caregiving increases. Symptoms can include difficulty with communication, disorientation to time and place, confusion, poor judgment, and behavioral changes. At late stages, people living with AD may have difficulty speaking, swallowing, and walking. Eventually, many people living with AD require around-the-clock in-home or institutional care. More than 11 million family members and other caregivers and other persons provided an estimated 16 billion hours of unpaid care to people with AD or other dementias, putting these caregivers at risk for negative mental, physical, and emotional outcomes.[2] The average life expectancy for people with AD depends on multiple factors including age, functional status at diagnosis, and comorbidities. Estimates range from 4 to 8 years, but some people with AD live as many as 20 years after diagnosis.[2]

Treatment of AD remains largely supportive, including creation and implementation of individualized 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 and supports (e.g., adult day care, caregiver training, etc.).[21] Non-pharmacologic treatments include physical activity, which some studies have suggested may prevent or mitigate AD[22,23] as well as behavioral and environmental strategies to ameliorate neuropsychiatric symptoms (e.g., agitation, delusions, disinhibition), and problem behaviors (e.g., resistance to care, hoarding, obsessive-compulsive behaviors).[24]

Pharmacological therapy of AD has until recently focused mainly on symptom management. The most commonly prescribed drugs are the cholinesterase inhibitors (AChEI), 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.[25,26]

Given the large and growing population of people 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 (Aduhelm™, Biogen), a human monoclonal antibody, was the first putative disease-modifying drug to obtain accelerated approval from the FDA in June 2021, based on PET-documented removal of amyloid from the brain. Since then, two additional anti-amyloid monoclonal antibodies have submitted applications for accelerated approval for the treatment of AD: lecanemab (Leqembi™, Eisai Co., Ltd) and donanemab (Eli Lilly & Co.). Lecanemab was approved on January 6, 2023 under accelerated approval and is the focus of this review. The manufacturer of donanemab received a Complete Response Letter for accelerated approval from the FDA on January 19, 2023. Therefore, although a prior version of the report contained a review of donanemab, we have removed it from this version.

Table 1.1. Interventions of Interest

Intervention	Mechanism of Action	Delivery Route	Prescribing Information
Leqembi™ (lecanemab)	Monoclonal antibody that binds to beta-amyloid protofibrils	Intravenous	10 mg/kg biweekly

mg: milligram, kg: kilogram

2. Patient and Caregiver Perspectives

ICER engaged with people living with Alzheimer's disease (AD) and caregivers, representatives from advocacy organizations, and clinical experts to understand the specific challenges associated with caring for persons with AD. We spoke with a total of 13 people with AD from across the US and across the disease spectrum (mild to severe), and in various living arrangements, and five caregivers from across the US with varied caregiving experiences (from early to late-stage AD). These were informal interviews; demographics of the sample are described further in the Supplement. We also drew on conversations from our 2021 Alzheimer's disease review.[27]

Individuals we spoke with emphasized the following issues, which are discussed in detail below: challenges with diagnosis, experience of coping with the diagnosis and a new way of living, impact on caregiver quality of life, treatment concerns and goals, and financial impacts and disparities.

Challenges with Diagnosis

Initial symptoms of AD may start many years prior to receiving a diagnosis starting with gradual cognitive decline[28] including difficulties with memory and executive function (a term that describes abilities of planning, flexible thinking, and focusing attention).[29,30] People with AD described forgetting meetings or names, getting lost, and feeling that something was "wrong"; sometimes they also received feedback from others who had noticed changes in behaviors. Caregivers also described that they began noticing subtle changes in their loved one's thinking and behavior, although sometimes identifying those changes was challenging if they did not live with the person with AD. Although an estimated 10% of people over the age of 65 are living with dementia due to AD, diagnosis is often missed or delayed. People with AD described the diagnosis process as long and, for some, complicated by confusion over whether their symptoms were due to AD or another medical condition. When receiving the diagnosis, some people with AD reported having a negative experience with their physician, such as being told to "get their affairs in order" or that they would decline rapidly. On the other hand, one person with AD reported that their physician told them to focus on living life fully which allowed them to continue to focus on activities they enjoyed (e.g., dancing and exercise).

After the diagnosis, lack of education about how to navigate the disease was described by both people with AD and caregivers. One person noted that "there needs to be more support when diagnosed. It is a complex process, especially when having other medical conditions to deal with." People living with AD reported wanting more information on such things as the disease and its course, clinical trials, and information on how the diagnosis can impact caregivers. 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, and information on end-of-life care was also lacking in many cases. Finally,

caregivers also reported on the lack of resources for them and having to educate themselves on AD to understand the best care for their loved one.

Experience of Coping with the Diagnosis and a New Way of Living

People living with AD described significant life changes after receiving the diagnosis. One person stated that their diagnosis "changed everything". Adjustments to daily life described to us included accepting more direction, using their phone to help with reminders, wearing headphones in noisy environments, moving to be closer to their family, and online grocery shopping. People with AD reported experiences of loss after the diagnosis, such as giving up certain activities, leaving their jobs, rehoming their animals, and confronting fears about loss of identity and the future loss of their independence. Depression, including suicidal thoughts, can also occur, and quality of life suffers even before severe memory deficit occurs. One person described that their "life has gone from a big platform to a small one." Coping mechanisms for the new changes in their lives included trying to maintain a positive attitude and staying busy, active, and social. AD also had an impact on relationships. People with AD described a loss of ability to be the type of relative they wished to be, such as wanting to look after their grandchildren, remembering special dates or birthdays, or developing new relationships.

Having AD is financially challenging, both because people with AD may have to stop working and because of challenges with navigating the system when applying for Social Security Disability Insurance (SSDI) or moving onto Medicare. Caregivers described taking control of their loved one's finances early and the challenges of getting access to services. Some caregivers reported that they were unable to gain access to all services and had to use their own funds to provide support for later stages (e.g., 24-hour in-home support to allow caregivers to continue to work, medications, clothes, or hobbies), which could also cause changes their financial circumstances.

Impact on Caregiver Quality of Life

The impact of AD on caregivers is substantial. Nearly half of all caregivers who provide care to older adults do so for someone with 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] Caregivers described that their caregiving responsibilities evolved over time and with stage of disease, and ranged from paying the bills and driving, and as the disease progresses to moderate-to-severe dementia and the patient loses function, assisting with activities of daily living such as bathing and dressing. Some caregivers were able to obtain support from other family members and elder services programs to help keep their loved ones living at home; others transitioned their loved ones to assisted living or nursing homes.

Caregivers described the emotional toll of caregiving, reporting that it was difficult to witness changes in how their loved one interacts with and experiences the world. One caregiver reported that it "took a while to realize that although part of her is still "mom", not everything that comes out of her mouth is really her… Those who aren't in the caregiving situation find it hard to understand where their heads are. [We may] come across as too pragmatic that we seem cold, but we all need to function, and this takes an incredible toll." Surveys have quantified the toll on caregivers - as individuals 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] 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. Several caregivers reported that there is not enough support available for their emotional and mental health needs and that there is variation in the degree of support available across the US for both patients and their caregivers.

When asked about their broader experience of caregiving, some caregivers describe the impact on their own life plans, including the ability to work and personal relationships. Caregivers described that because of their caregiving responsibilities, they have had less time for their own family, such as fewer vacations or leisure activities. Some caregivers reported resigning from their jobs to be a caregiver, as they were unable to manage both caregiving and job responsibilities. Another caregiver reported that they had to spend time away from their family to care for their loved one with AD which caused strain on their relationship at home. One caregiver described that "I feel like I haven't had the chance to live my life" and another caregiver told us that "[Person with AD] has often asked me if I am going to have kids… that is the only thing that may have stopped."

Treatment Concerns and Hopes

People with AD and caregivers would like more options for treatments. The main goal of treatment is not to cure, but to slow or halt the progression of the disease and maintain their current level of functioning (e.g., independence, hobbies, personal care) as long as possible. One patient described that "more time doesn't do it for me. I would say more quality time".

In terms of anti-amyloid therapies, both people living with AD and caregivers were interested in any treatment that would help slow disease progression. However, both groups described concerns about the side effect of brain swelling and questioned whether the gains in quality of life that might be seen with treatment outweighed that risk. There were also logistical concerns about a treatment with regular infusions, particularly for those persons who do not drive, and concerns about an increased burden on caregivers. Caregivers also reported treatment accessibility issues due to the location of medical centers, the limited number of physicians and health systems offering treatment and concerns about insurance coverage [in the context of aducanumab], and concern over their loved one experiencing pain or anxiety from the infusion.

Disparities in Clinical Care and Research

Both people with AD and caregivers raised concerns surrounding disparities in clinical care and research. For example, although African Americans make up only around 9% of the US population, they represent 13.8% of persons with dementia, with Black women having the highest prevalence. Black persons are more likely to experience neuropsychiatric symptoms, behavioral changes such as agitation and aggression, abnormal sleep, and motor disturbances.[31] Furthermore, Black persons are more likely to be diagnosed with dementia at a later stage.[31] There are also inequities in caregiving, with Black and Hispanic caregivers more likely to provide a high intensity level of care, and Black caregivers more likely to be the sole unpaid caregiver for their care recipient and less likely to receive respite services and information from medical care providers.[32,33]

Both people with AD and caregivers raised concerns about the limited or culturally misaligned information provided to communities of color about AD or how to provide care for loved ones with AD, and believed that more resource sharing and more support group leaders who are people of color could raise awareness in the community. In particular, increasing awareness about the Improving HOPE for Alzheimer's Act of 2020,[34] which aims to increase use of comprehensive care planning through education of clinicians, patients, and caregivers, could improve access to care. Broader access to effective therapies and increasing diversity among providers for dementia care could also help address disparities in treatment.

People living with AD noted that "everyone should have the right to participate in clinical trials" but that people of color are less likely to be able to participate due to having other medical comorbidities, location of the clinical trials, or not having a care partner. Patient groups pointed to a need to engage, recruit, and retain diverse populations in Alzheimer's research and clinical trials to help decrease health inequities.

3. Comparative Clinical Effectiveness

3.1. Methods Overview

Scope of Review

We reviewed the clinical effectiveness of lecanemab, in addition to supportive care, versus supportive care alone for the treatment of individuals with early Alzheimer's Disease (AD) (i.e., MCI due to AD and mild dementia due to AD) with evidence of AD pathology. We sought and reviewed evidence, where available, on patient-important outcomes, including change in the ability to maintain independence and cognitive function and perform activities of daily living, as well as delaying entry into institutional care, quality of life, caregiver impact, and behavioral change. We also reviewed evidence on changes in biomarkers (e.g., level of beta-amyloid, level of tau and phosphorylated tau [p-tau], and brain volume). We also aimed to evaluate updated evidence for aducanumab that was not covered in the previous August 2021 review.[8] We found no new clinical evidence for aducanumab that would have affected our assessment and thus it is not reviewed in this report. The full scope and procedures for the systematic literature review are detailed in the supplement.

Evidence Base

Lecanemab

Evidence informing our review of lecanemab was derived from one Phase III randomized controlled trial (RCT): CLARITY AD. We also reviewed the lecanemab Phase II trial (G000-201), but because there were differences in the trial objectives, dosing, and design, it was not a primary focus of our review. G000-201 is described in Section D of the Supplement.

CLARITY AD was a Phase III placebo-controlled RCT that evaluated the efficacy of 10 mg/kg of intravenous lecanemab administered every two weeks versus placebo for 18 months, with an open-label extension phase with all participants receiving lecanemab for an additional 27 months.[35] The primary outcome was change from baseline in CDR-SB at 18 months. The open-label extension phase examined treatment-emergent adverse events and change in CDR-SB. Participants were included if they were aged between 50 and 90 years and had a mild cognitive impairment due to Alzheimer's disease or mild Alzheimer's disease dementia, objective impairment in episodic memory, amyloid positivity as determined by PET or CSF (Aβ1–42), objective impairment in episodic memory, had a Mini-Mental State Exam (MMSE) score of 22-30, BMI 17-35, and, if they were receiving any treatment for AD symptoms, were on a stable dose for 12 weeks prior to baseline. Full inclusion and exclusion criteria are described in Table D3.1. in the Supplement. Baseline characteristics and cognitive scores for CLARITY AD are outlined in Table 3.1.

ARIA was assessed by MRI at baseline and five additional time points across the study and presence of ARIA could have led to the study drug being held or discontinued.

Table. 3.1. Baseline Characteristics and Cognitive Measures for CLARITY AD[35]

Baseline Characteristics and Cognitive Scores	N=1795 (lecanemab, N=859, placebo, N=875*)
Age in Years, Mean (SD)	71.2 (7.9)
Sex, Female %	52.3%
Race/Ethnicity	76.9% White, 2.5% Black, 17% Asian, 3.7% Other, 12.4% Hispanic
Concomitant AD medication	52.8% AChEI or memantine
ApoE ε4 Carrier **ApoE ε4 Heterozygote** **ApoE ε4 Homozygote**	68.8% 53.3% 15.5%
Stage of Disease	61.9% MCI due to AD and 38.1% Mild AD
MMSE, Mean (SD) (Range)	25.6 (2.2) (22-30)
CDR-SB, Mean (SD) (Range)	3.2 (1.34) (0.5-8.5)
ADAS-Cog14, Mean (SD) (Range)	24.4 (7.32) (4.7-60.7)
ADCS-MCI-ADL, Mean (SD) (Range)	41.1 (6.75) (12-53)
ADCOMS, Mean (SD) (Range)	0.399 (0.147) (0.07-0.94)
Baseline Beta-amyloid, Mean Centiloids (SD)	76.48 (43.3)†

AChEI: acetylcholinesterase inhibitor, AD: Alzheimer's disease, ADAS-Cog 14: Alzheimer's Disease Assessment Scale–Cognitive Subscale 14-item, ADCOMS: AD composite score, ADCS MCI-ADL: Alzheimer's Disease Cooperative Study – Activities of Daily Living Inventory (MCI version), ApoE: apolipoprotein E, CDR-SB: Clinical Dementia Rating scale Sum of Boxes, MMSE: Mini-Mental State Examination, SD: standard deviation

*mITT population

†Included only participants enrolled in the PET substudy (N=354 lecanemab and N=344 placebo)

3.2. Results

Clinical Benefits

In this report, we describe the change in cognitive function, health-related quality of life, beta-amyloid, and other biomarkers (tau, p-tau, and brain volume) from baseline to 18 months after treatment initiation for lecanemab. A variety of cognitive measures were used across the trials. In Section A1 of the Supplement, we provide definitions of each of the cognitive outcomes. Table 3.2. provides minimal clinically importance differences (MCID) in the published literature associated with cognitive outcomes used across the trials, although there is not universal agreement on what constitutes a clinically relevant change for persons with AD. While MCID applies to changes for a specific patient, when averaged in aggregate it can provide context for the magnitude of changes overall. It is important to remember, though, that if patient responses are normally distributed, half of patients will have outcomes better than the average and half worse than the average. We discuss results for lecanemab in the context of MCIDs to help contextualize whether statistically significant results may also be clinically relevant, as statistical significance can be a reflection of sample size, a clinically relevant change, or both.

Table 3.2. Minimal Clinically Importance Differences for Cognitive Outcomes

Cognitive Outcome	Minimal Clinically Important Difference (MCID)
Clinical Dementia Rating – Sum of Boxes (CDR-SB)	Change of 0.98-1.63 for MCI due to AD and mild AD dementia.[36]
Alzheimer's Disease Assessment Scale – Cognitive Subscale (ADAS-Cog), including ADAS-Cog-13 and ADAS-Cog14.	Change of 2 points for MCI due to AD[37] and ≥3 points for mild AD.[38,39]
Alzheimer's Disease Cooperative Study – Activities of Daily Living Inventory (MCI version) (ADCS-MCI-ADL)	There are no data on MCID.
AD Composite Score (ADCOMS)	There are no data on MCID.

AD: Alzheimer's Disease, MCI: Mild cognitive impairment

Lecanemab

Cognitive outcomes

The primary outcome in CLARITY AD trial was the change from baseline in CDR-SB score at 18 months. Participants treated with lecanemab had 27% less decline in CDR-SB compared to placebo at 18 months, with a mean difference of -0.45; 95% CI: -0.67 to -0.23; p<0.001[35] (Table 3.3.). This mean difference in CDR-SB was less than what some consider as MCID for the scale.[36,40] Changes in CDR-SB remained fairly consistent across the sensitivity analyses that imputed data, included all randomized participants, or censored assessments after ARIA-E had occurred (Supplement Table D3.22).[35]

Other measures of cognition assessed in the trial also showed statistically significant differences favoring the lecanemab treated group (Table 3.3.). Participants treated with lecanemab had less decline in ADAS-Cog14 compared to placebo at 18 months, with a mean difference of -1.44; 95% CI: -2.27 to -0.61; p<0.001[35], less than the 2-3 point change considered as the MCID for this scale for people with MCI and mild AD.[38,39] Those treated with lecanemab also had less decline in ADCS-MCI-ADL compared to placebo, with a mean difference of 2.0; 95% CI: 1.2 to 2.8; p<0.001.[35] and less decline in ADCOMS compared to placebo, with a mean difference of -0.05; 95% CI: -0.074 to -0.027; p<0.001.[35] This mean difference for ADCOMS was the same as that reported in the Phase II G000-201 trial.

Health-Related Quality of Life

Definitions of health-related quality of life scales are provided in Section A of the supplement. Changes in health-related quality of life measures were available for around 85% of participants at 18 months. For participant-reported outcomes, participants in the lecanemab group had 49% less decline on European Quality of Life – 5 dimensions (5 level version) (EQ-5D-5L) at 18 months compared to placebo (p<0.01). There was also 56% less decline on the Quality of Life in Alzheimer's Disease (QOL-AD) in the lecanemab group compared to the placebo group (p<0.01).[41] For caregiver-reported outcomes, caregivers of participants in the lecanemab group reported 38% less decline on Zarit Burden Interview at 18 months compared to placebo (p<0.001) and 23% less decline on the QOL-AD (subject by proxy) compared to placebo (p<0.05).[41] See Supplement Table D3.4.

Beta-Amyloid Levels

Changes in beta-amyloid, as measured in centiloids using florbetaben, florbetapir, or flutemetamol PET tracers, were assessed in a substudy including 698 participants (n=354 in lecanemab and n=344 in placebo). At 18 months, participants in the lecanemab group had a larger amount of beta-amyloid removed compared with the placebo group (mean difference -59.12; 95% CI: -62.64 to -55.60; p<0.001),[35] corresponding to a calculated mean percentage difference versus placebo of -76.0%. Additionally, at 18 months, 32.4% of those in the lecanemab group were amyloid negative (defined as having <30 centiloids on PET scan) compared to 7.8% in the placebo group.[42] CSF and plasma markers of Aβ42/40 were also consistent with amyloid removal in the lecanemab group. Descriptions of assessment and findings for Plasma and CSF measures of amyloid are in provided in Section D of the Supplement.

Other Biomarker Outcomes

There were statistically significant reductions in several tau biomarkers in the lecanemab treated group (CSF t-tau and CSF and plasma p-tau) in the lecanemab group, compared with the placebo group at 18 months[35] (Supplement Table D3.4). In terms of brain volume, there was greater decrease in whole brain volume and a greater increase in ventricular volume in the lecanemab

group compared to the placebo group at month 18. There was less atrophy in hippocampal volume in lecanemab as compared to placebo.[42] At the time of this draft report, the investigators note that tau PET and volumetric MRI results have not been fully analyzed[35] and thus interpretation of these outcomes are limited. Detailed descriptions of these assessments and results of other biomarkers are in provided in Section D of the Supplement.

Table 3.3. Key Trial Results

Measure		CLARITY AD[35]	
		Lecanemab	Placebo
CDR-SB	Baseline (SD) (Range)	3.17 (1.34) (0.5 to 8.0)	3.22 (1.34) (0.5 to8.5)
	Timepoint	18 months	
	N	714	757
	Mean Change	1.21	1.66
	Difference in Mean Change (95% CI)	-0.45 (-0.67 to -0.23)	REF
ADAS-Cog14	Baseline (SD) (Range)	24.45 (7.08) (4.7 to 47.7)	24.37 (7.56) (5.0 to 60.7)
	Timepoint	18 months	
	N	703	738
	Mean Change	4.14	5.58
	Difference in Mean Change (95% CI)	-1.44 (-2.27 to -0.61)	REF
ADCOMS	Baseline (SD) (Range)	0.398 (0.147) (0.08 to 0.94)	0.400 (0.147) (0.07 to 0.91)
	Timepoint	18 months	
	N	708	749
	Mean Change	0.164	0.214
	Difference in Mean Change (95% CI)	-0.05 (-0.074 to -0.027)	REF
ADCS-MCI-ADL	Baseline (SD) (Range)	41.2 (6.6) (13 to 53)	40.9 (6.9) (12 to 53
	Timepoint	18 months	
	N	676	707
	Mean Change	-3.5	-5.5
	Difference in Mean Change (95% CI)	2.0 (1.2 to 2.8)	REF

ADAS-Cog 14: Alzheimer's Disease Assessment Scale–Cognitive Subscale 14-item, ADCOMS: AD composite score, ADCS MCI-ADL: Alzheimer's Disease Cooperative Study – Activities of Daily Living Inventory (MCI version), CDR-SB: Clinical Dementia Rating scale Sum of Boxes, SD: standard deviation

Harms

Lecanemab

Total adverse events and serious adverse events were slightly higher in the lecanemab versus placebo group (Table 3.4.) in the CLARITY AD trial. There were 6 deaths in lecanemab treated group and 7 deaths in placebo group, with myocardial infarction, cerebral macrohemorrhage, cerebrovascular accident, respiratory failure, and COVID-19 listed among the causes of death in both groups.[35] There were no deaths directly attributed to ARIA in either group. Discontinuation in CLARITY AD was lower than the Phase II (G000-201) trial, and fairly similar across groups (lecanemab: 18.8% versus placebo: 15.6%). The most common reasons for discontinuation were

adverse events, withdrawing consent, and choosing to discontinue from treatment regimen. Discontinuation of treatment due to adverse events were higher in lecanemab (6.9% vs. 2.9%) as were discontinuation of trial due to adverse events (5.7% vs. 3.1%) (Table 3.4). Participants in the lecanemab group also reported more infusion-related reactions compared to the placebo group (26.4% vs 7.4%). [35]

ARIA due to edema or effusion (ARIA-E) or brain microhemorrhage or localized superficial siderosis reflecting prior hemorrhage (ARIA-H) were of interest to the review. A total of 21.5% participants in the lecanemab group experienced either ARIA-E or ARIA-H, compared to 9.5% in the placebo group (Table 3.4., Supplement Table D3.11).

As expected, ARIA-E occurred more often in the lecanemab group compared with placebo (12.6% vs 1.7%), and 2.8% of participants in the lecanemab group experienced symptomatic ARIA-E (e.g., headache, visual disturbance, or confusion or severe radiographic changes on MRI). ARIA-E occurred more frequently in ApoE ε4 carriers compared to non-carriers in the lecanemab treated group (3.4% vs 1.4%), and also occurred more in ApoE ε4 homozygotes compared to heterozygotes (9.2% vs 1.7%).[35] ARIA-E generally occurred in the first three months of treatment (71%), was mostly mild-moderate in severity, and the investigators reported that 81% of ARIA-E resolved within four months.[43] Seven participants (0.8%) in the lecanemab group had a significant adverse event (SAE) associated with ARIA-E. Recurrent ARIA-E occurred more often in the lecanemab group compared with the placebo group (3.1% vs 0.1%, Supplement Table D3.11).

ARIA-H, which was mainly due to cerebral microhemorrhage, occurred more frequently in the lecanemab group compared with placebo (17.3% versus 9.0%); very few cases of ARIA-H were symptomatic (0.7% in lecanemab and 0.2% in placebo). ARIA-H was more likely to co-occur with ARIA-E in the lecanemab group (8.2%) compared to placebo (1.0%).[35] Like ARIA-E, ARIA-H occurred more frequently in ApoE ε4 carriers compared with non-carriers (19.7% versus 11.9% in the lecanemab treated group) and was more frequent in ApoE ε4 homozygotes compared to heterozygotes (39% versus 14%).[35] Unlike ARIA-E, which occurred early in the study period, ARIA-H occurred randomly across the study period.[43] There was one reported case of cerebral macrohemorrhage that occurred 30 days after stopping the study drug and thus its relationship to lecanemab treatment is uncertain.

Full data are not available from the open-label extension (OLE) phase of CLARITY AD. During this phase, safety assessments were conducted every 6 months. The safety MRI schedule initially followed the same schedule as the core phase for 6 months (weeks 9, 13, and 6 months) and reduced to every 6 months thereafter. At the time of posting this report, three deaths have been reported in the lecanemab group due to cerebral macrohemorrhage (0.1%). One participant was reportedly on the anticoagulant apixaban and one participant was given tissue plasminogen activator (tPA) while being treated for an acute stroke.[43-45] The third participant received lecanemab during the OL and had what appeared to be severe symptomatic ARIA-E and ARIA-H

with cognitive dysfunction and seizures, and died days later.[46] The trial sponsor reports that they are still investigating whether this death is related to lecanemab treatment.[46]

Table 3.4. Adverse Events

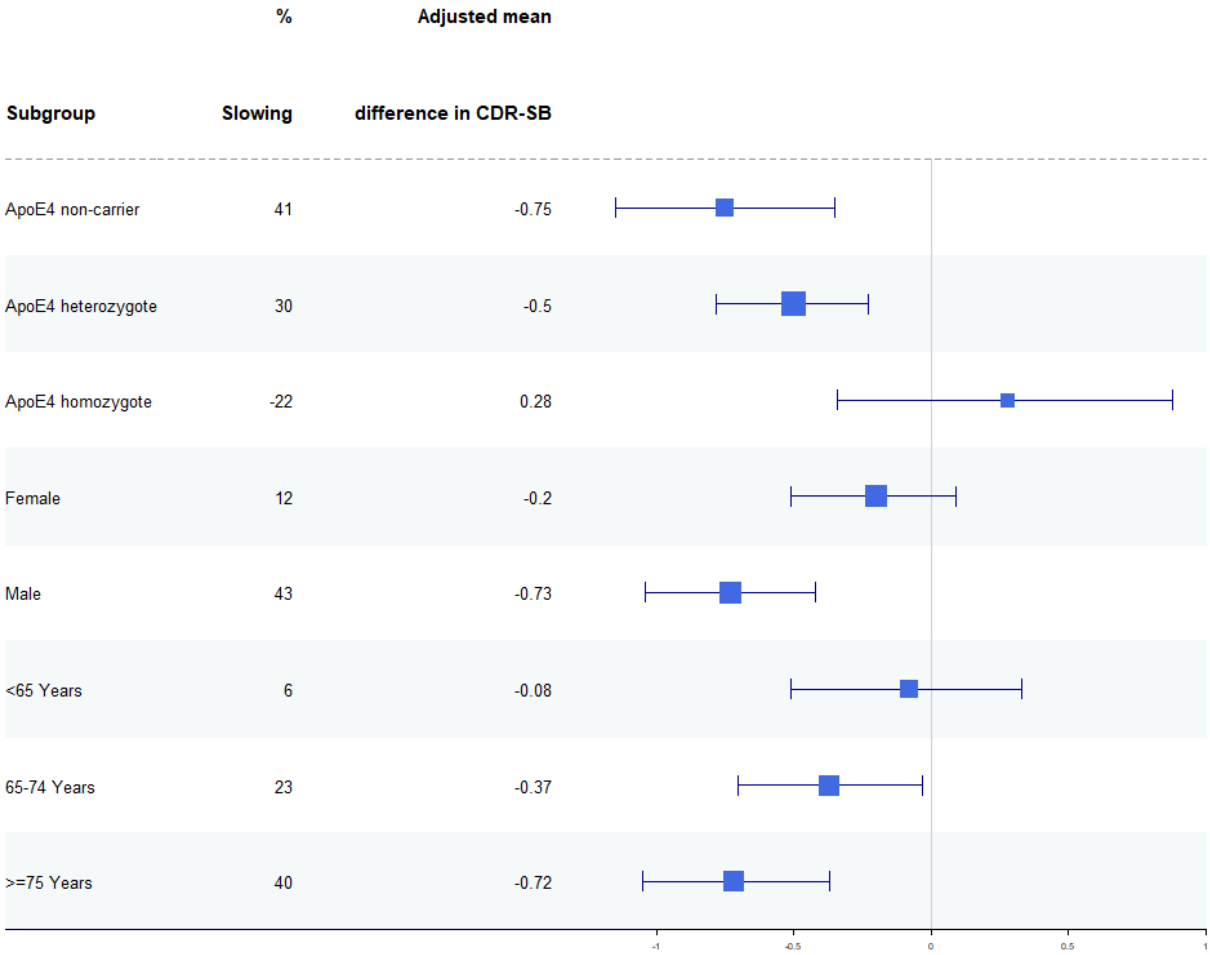
Harms	CLARITY AD[35]	
	Lecanemab	Placebo
Any Adverse Event, n/N (%)	798/898 (88.9%)	735/897 (81.9%)
Serious Adverse Event, n/N (%)	126/898 (14.0%)	101/897 (11.3%)
Discontinuation Due to Adverse Event, n/N (%)	62/898 (6.9%)*	26/897 (2.9%)*
Any ARIA-H, n/N (%)	155/898 (17.3%)	81/897 (9.0%)
Any ARIA-E, n/N (%)	113/898 (12.6%)	15/897 (1.7%)
Symptomatic ARIA-E, n/N (%)	25/898 (2.8%)	0/897 (0%)

ARIA-E: amyloid-related imaging abnormalities due to edema/effusion, ARIA-H: amyloid-related imaging abnormalities due to hemorrhage or superficial siderosis, N: total participants, n: number of participants
*Per the protocol, primary reasons for any discontinuation from the study are: AE, lost to follow-up, subject choice, withdrawal of consent, pregnancy, study terminated by sponsor, and other.

Subgroup Analyses and Heterogeneity

CLARITY AD trial included a more racially and ethnically diverse sample than previously published Alzheimer's disease trials, see below for full evaluation of clinical trial diversity. In the CLARITY AD trial, over half the sample had two or more comorbidities (e.g., diabetes, hypertension, etc.) and 4.5% were on anticoagulants, more closely representing participants who may seek this therapy in real-world clinical settings. Prespecified subgroup analyses were conducted on the cognitive outcomes across various subgroups of interest. There were four subgroup analyses that appeared to have consistent results across the cognitive measures. The effect of lecanemab on cognitive outcomes appeared to vary across ApoE ε4 carrier status, with lecanemab showing a larger effect in ApoE ε4 noncarriers compared to carriers and having the least effect in ApoE ε4 homozygote participants, particularly on the CDR-SB and ADCOMS measures. When disease state was examined, there was similar relative change in CDR-SB in MCI compared with mild AD (28% versus 27% change, respectively). There was a trend towards greater slowing of decline in older participants (≥75 years) compared to younger participants (<65 years) in 3 of the 4 cognitive outcomes. Finally, male participants showed a greater slowing of decline compared to female participants.[47] See Figure 3.1. For CDR-SB specifically, the treatment effect remained consistent across participants with comorbidities, such as hypertension, diabetes, heart disease (Supplement Table D3.17).[41] Detailed results on subgroups are presented in Supplement Tables D3.18-23 and additional subgroups are described in Supplement D2. Caution must be taken in the interpretation of these subgroup effects as they were likely underpowered and did not correct for multiplicity.

Figure 3.1. Forest Plot of Subgroup Analyses for CDR-SB at 18 Months (Age, ApoE ε4 Genotype, and Sex)



Evaluation of Clinical Trial Diversity

Table 3.5. Sample Diversity Ratings on Race and Ethnicity, Sex, and Age (Older Adults)

Trials	Race and Ethnicity (All Participants)	Race and Ethnicity (US subgroup)	Sex	Age (Older adults)
G000-201 (Phase II)	Poor	NR	Good	NE
CLARITY AD (Phase III)	Fair	Fair	Good	NE

NE: Not Estimated, NR: Not Reported.

We evaluated the demographic diversity of the clinical trials using the ICER-developed diversity rating tool. Table 3.5. presents sample diversity ratings on race and ethnicity, sex, and age (older adults) on the two key trials in our review. Details on each of the demographic categories are

provided below. Additional details on the clinical trial diversity rating tool and detailed information on the scores and rating of each trial are provided in Supplement D1.

Race and Ethnicity: The Phase II trial did not report any data on race and ethnicity and thus was rated as "poor." The Phase III CLARITY AD trial, which we rated as "fair" on racial and ethnic diversity, had an adequate representation of White and Asian individuals compared to the disease prevalence; however, Black or African American and Hispanic or Latino individuals were underrepresented. Because the CLARITY AD trial was a multinational study, we also separately evaluated the subpopulation of patients enrolled in the US. Compared to the disease prevalence, White and Hispanic individuals were adequately represented in the US subpopulation of the CLARITY AD trial, while Black or African American and Asian individuals were underrepresented. Thus, similar to the overall population, we rated the US subpopulation in the CLARITY AD trial as "fair" on racial and ethnic diversity. See Supplement Tables D1.9.-D1.11.

Sex: Both trials adequately represented males and females; therefore, both trials were rated as "good."

Age: As Alzheimer's disease typically develops in older adults, we did not attempt to assess diversity in terms of age.

Uncertainty and Controversies

If the amyloid hypothesis is correct, it would be expected that removal of amyloid should be associated with treatment effect. For lecanemab we do not yet have adequate data showing such correlations (see Supplement Table D3.24.) or data showing differences in outcomes by achieving or not achieving amyloid negativity. Additionally, published systematic literature reviews that have incorporated both published and unpublished trials on anti-amyloid medications report that, while these medications were effective at reducing beta amyloid in the brain, the effect on slowing cognitive decline was inconsistent.[48-50] However, limitations of those reviews such as lack of full data availability and presentation of only aggregated data, prevents assessments of heterogeneity in response to amyloid reduction and slowing of cognitive decline.[51] See Supplement D5 for summaries of these reviews.

MCID refers to changes within a specific patient. Aggregate measures, such as mean change in an outcome, will potentially obscure changes in individual patients that are above or below the MCID. It would be helpful in assessing magnitude of benefit relative to clinical benefit if manufacturers provide analyses of the percentage of patients who experience decreases in an outcome measure beyond a prespecified endpoint (percentage clinically important decline, for instance) in the placebo and treatment groups. However, with or without such an analysis, unless changes in the assessed outcome measure are very non-normally distributed, comparison to MCID will be helpful to those assessing the data in understanding the magnitude of benefits for patients.

There have been concerns among experts that improvements seen in trials of anti-amyloid therapies may reflect "functional unblinding". This could occur on subjective scales when patients, caregivers, and providers recognize that a patient who develops ARIA is very likely receiving an active treatment rather than placebo. As noted in our prior report, the best approach to this would be to ensure that there are equal numbers of patients managed as if they had developed ARIA in the placebo arm so as to maintain blinding. As this was not done, ICER reviewed data across trials (data not shown) to see if frequency of ARIA correlated with benefit. We did not find such a correlation and so continue to consider it relatively unlikely that the results seen in trials of anti-amyloid therapies are due to functional unblinding.

The FDA accepted a statistically significant change in CDR-SB in the aducanumab trials as sufficient evidence of benefit to proceed with accelerated approval; however, experts disagree on this point.[7,52] Some experts have suggested that the minimal clinically important difference (MCID) for CDR-SB is on the order of 1 or 2 points.[36] Others suggest that MCID only reflects mean group differences and does not capture patient-level change and thus may not accurately reflect benefit to individual patients.[53] Thus, the absolute difference in CDR-SB of 0.45 points between groups, while statistically significant, may or may not result in a change in status that is meaningful to individual patients and caregivers. A recent web-based survey to individuals at risk for or with AD reported that concepts that were meaningful to them went beyond cognition and functioning alone, and expanded to desire to maintain independence, emotional wellbeing, safety, and physical and mental health, which are currently not well captured in measures used in clinical trials of AD patients such as CDR-SB.[54] In CLARITY-AD, assessments of patient and caregiver quality of life in CLARITY-AD do suggest measurable differences due to treatment with lecanemab; further details and longer-term follow-up are needed to fully understand the potential benefits of lecanemab treatment on this domain.

Even in people with cognitive abnormalities and imaging showing amyloid, some individuals likely have other causes of dementia.[55] A treatment that removes amyloid would have been anticipated to be most effective in patients least likely to have other forms of dementia. Patients who are older and male are at higher risk for vascular dementia, and APOE ε4 is a known risk factor for AD. As such, older male participants without APOE ε4 would be more likely to form a group in CLARITY-AD that has more vascular dementia (and possibly other non-Alzheimer's-type dementia). However, the actual subgroup analyses in CLARITY-AD show just the opposite (see Figure 3.1.). This is in contrast to the EMERGE trial for aducanumab, where similar changes in CDR-SB were seen overall, but where APOE ε4 carriers had greater improvement than non-carriers.

While a substantial percentage of participants treated with lecanemab reached amyloid negativity by PET scan, it should also be noted that 7.8% of participants in the placebo group were also amyloid negative at the end of the trial. This points to the complexity of the pathophysiology of AD and underscores that we do not fully understand the role of amyloid in AD and what factors (e.g.,

degree or rate of amyloid removal, a threshold of amyloid removal, or removal of certain amyloid subspecies) may impact clinical outcomes.

The effectiveness of lecanemab in people with moderate or severe AD is unknown, as the drug was not studied in these groups. It is uncertain whether treatment should be continued indefinitely or discontinued either when a certain degree of amyloid clearance is attained or at a specific point in the course of the disease.

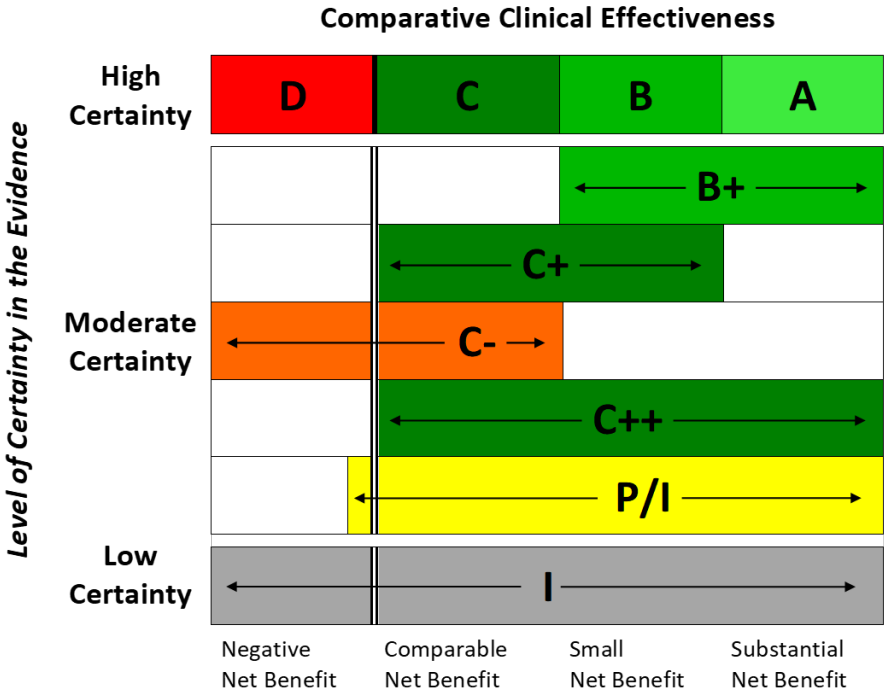
ARIA is the major adverse effect seen with anti-amyloid therapies. Risks of ARIA in real world use may be greater than was seen in clinical trials given issues including that participants in clinical trials typically do better than randomly selected patients, clinical expertise is likely to be less in real world use, and labeling is unlikely to require the intensity of MRI monitoring that was done in CLARITY-AD. Furthermore, concerns about an increased risk of cerebral hemorrhage with concomitant use of anticoagulants have heightened with the report of three deaths in the lecanemab open label extension study in participants receiving anticoagulation.

The average age of participants in CLARITY-AD was 71.2 years and included participants with some comorbidities. However, since two-thirds of individuals in the US with AD are 75 years old or older, who are also more likely to have significant comorbidities, the trial results may not be generalizable to the broader Alzheimer's population.

3.3. Summary and Comment

An explanation of the ICER Evidence Rating Matrix (Figure 3.2) is provided in the Supplement.

Figure 3.2. 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*

The FDA approval of aducanumab, the first disease-modifying therapy for AD in June of 2021, based on biomarker evidence of beta-amyloid removal but with inconsistent clinical benefit from identically designed trials, brought forth several controversies, including how extensively amyloid is involved in the pathogenesis of AD and whether removal could result in meaningful clinical benefit, how to interpret outcomes from trials with protocol changes and that were stopped early for futility, and how great the risk of ARIA and its potentially severe consequences may be with use in the real world with less monitoring than clinical trials. Many prior anti-amyloid drugs have not

demonstrated clinical benefits, and results reported subsequent to the approval of aducanumab were also negative for crenezumab and gantenerumab. Although it is possible to interpret these results as showing that inadequate amyloid was removed by those two therapies to achieve benefit, it is also possible that there is something specific to lecanemab's mechanism of action that resulted in cognitive benefits, alone or in combination with amyloid removal. We do not feel that evidence is adequate at this point to assume that clearance of amyloid will necessarily improve cognitive outcomes. Patient-level evidence across trials and agents showing that degree of amyloid removal correlates with clinical benefit would be an important step in establishing amyloid removal as an important surrogate outcome, although even then, surrogate endpoints may fail to predict the effect of treatment on a clinical outcome, either due to the complexity of disease pathophysiology or unintended effects on other outcomes.[56]

Since removal of amyloid remains unproven as a surrogate outcome, it is important to look to clinical outcomes directly. Any cognitive benefits seen with an anti-amyloid therapy must be weighed against harms, and particularly the risk of ARIA.

CLARITY AD, a Phase III trial testing the efficacy of lecanemab, is the first clinical trial of an anti-amyloid antibody to clearly demonstrate that amyloid clearance is associated with a slowing of cognitive decline in participants with early AD. The 27% relative change in CDR-SB is similar to the change seen in EMERGE, the positive aducanumab trial. The CLARITY AD trial also showed positive results on other cognitive, MRI, and biomarker outcomes and on patient and caregiver quality of life, consistent with the primary outcome. However, whether the absolute change in CDR-SB, the primary outcome in the trial, is clinically relevant remains less certain. As a comparison, one RCT of donepezil 10 mg showed a statistically significant change in CDR-SB compared with placebo over 24 weeks of treatment (-0.60, p=0.0007).[57] Additionally, as discussed above (see Figure 3.1 showing subgroup forest plots), we have some concerns that cognitive benefits were greatest in the subgroup of participants most likely to have included participants with other etiologies of dementia. As such, we have some concerns that lecanemab's mechanism of action may not be fully understood. Given all this, and the many prior negative trials of anti-amyloid therapies, we have some remaining uncertainties even about clinical benefits when looking at a single randomized trial.

Rates of ARIA were less than seen in the aducanumab trials. Although there was no significant difference in the rate of death during the core clinical trial, there were three recently reported deaths in the open label extension trial, and thus we remain concerned that real world ARIA occurrences and consequences may be more severe if, as expected, monitoring MRIs are not as frequent as in the clinical trial, the patient population treated differs from the trial population, and clinicians are less expert than those who participated in the randomized trial.

In aggregate, the net health benefits of lecanemab in participants with early AD may be small or even substantial, but there remains a possibility of net harm from ARIA. We rate treatment with lecanemab in MCI due to AD or mild AD as "Promising but Inconclusive" (**P/I**).

Table 3.6. Evidence Ratings

Treatment	Comparator	Evidence Rating
Patients with Early Alzheimer's Disease		
Lecanemab	Supportive care	P/I

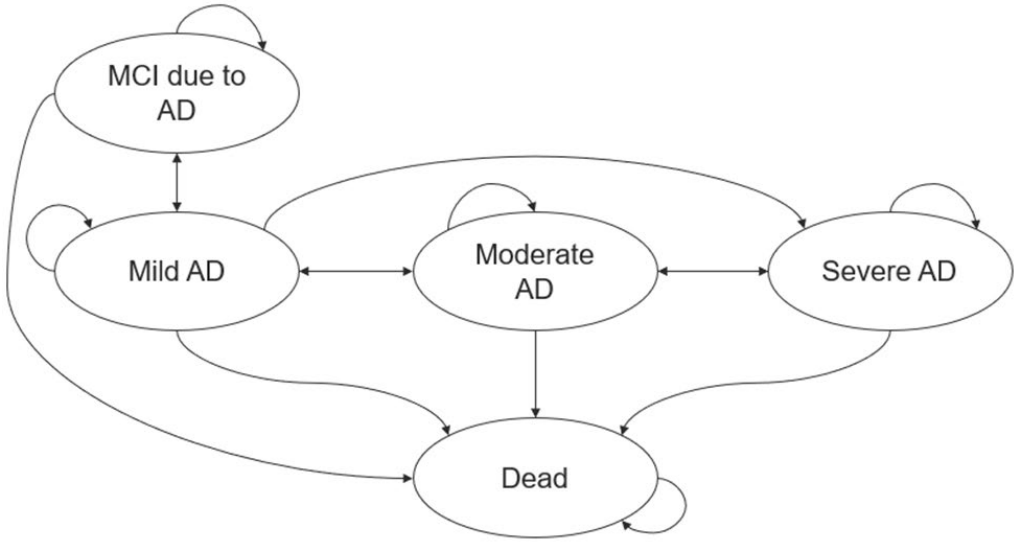
4. Long-Term Cost Effectiveness

4.1. Methods Overview

The primary aim of this analysis was to estimate the lifetime cost effectiveness of lecanemab in addition to supportive care as compared to supportive care alone. Supportive care could include non-pharmacologic and pharmacologic, but not disease-modifying, interventions. We report results from two perspectives: a health care sector 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). In alignment with our approach from our prior AD review, these perspectives are presented as co-base-case analyses given the enormity of the societal costs in AD.

We adapted our AD decision analytic model developed for our prior AD assessment that included aducanumab.[8] The model consisted of five health states that tracked the severity of disease, including mild cognitive impairment (MCI) due to AD, mild AD, moderate AD, severe AD, and death. Figure 4.1. on the following page displays each of these health states and the possible transitions between them. Patients in the MCI due to AD health state could progress to the mild AD health state or stay in the MCI due to AD health state. Individuals in the mild AD health state could either stay in the mild AD health state, progress to either the moderate AD or severe AD health states or revert back to the MCI due to AD health state. Individuals in the moderate AD health state could either stay in the moderate AD health state, progress to the severe AD health state, or revert to the mild AD health state. Individuals in the severe AD health state could either stay in the severe AD health state or revert to the moderate AD health state. All health states could transition to the death health state due to all-cause or disease-specific mortality. Model cycle length was one year as has been used in prior published economic models and in clinical evidence.[58-61] Specific to each health state, the model also tracked the setting of care (e.g., community or long-term care). Patients could transition from community to long-term care; however, once in long-term care, they remained there over the lifetime time horizon. The model was developed in Microsoft Excel.

Figure 4.1. Model Structure



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

The model included a hypothetical cohort of patients with MCI due to AD or mild AD entering the model and receiving either the intervention or comparator treatments. The hypothetical cohort had amyloid positivity confirmed by a reliable method prior to initiating treatment. Baseline population characteristics can be found in the Supplement. 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. Model outcomes included quality-adjusted life years (QALYs), equal-value life years (evLYs), life years (LYs), years living outside of long-term care, and costs over a lifetime time horizon. All future costs and outcomes were discounted at 3% per year.

Since the posting of our draft report, we have removed donanemab from this assessment because the manufacturer announced they received a complete response letter for accelerated approval. Additionally, we have updated the baseline characteristics of the model to no longer include evidence from donanemab and we have updated the price for lecanemab now that the wholesale acquisition cost is available.

4.2. Key Model Assumptions and Inputs

Table 4.1. reports model assumptions along with their rationale that are important to consider when interpreting the findings. A full list of model assumptions can be found in the Supplement.

Table 4.1. Key Model Assumptions

Assumption	Rationale
Lecanemab was effective at slowing the progression of disease while a patient had MCI due to AD or mild AD. Lecanemab was no longer effective once a patient reached moderate AD.	The evidence on clinical outcomes that exists for lecanemab is in early AD. Based on trials of anti-amyloid therapies suggesting no benefit in moderate AD, clinical experts suggested there is likely no effect with anti-amyloid therapies at reducing disease progression once a patient has reached moderate AD. This assumption was tested in scenario analyses.
Patients stopped receiving lecanemab treatment once they reached moderate AD.	Based on trials of anti-amyloid therapies suggesting no benefit in moderate AD, clinical experts suggested there is likely no effect with these anti-amyloid treatments at reducing disease progression once a patient has reached moderate AD, and therefore in our model, treatment stopped once a patient reached moderate AD. In a scenario analysis, we modeled patients stopping treatment once they reached severe AD. Robust evidence is lacking on lecanemab's effect on clinical outcomes after a patient has stopped the treatment, and thus no additional clinical benefit was assumed after a patient stopped treatment.
All occurrences of ARIA and its associated consequences (on cost, quality of life, and treatment discontinuation) were modeled in the first year of treatment.	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.

AD: Alzheimer's disease, CDR-SB: Clinical Dementia Rating-Sum of Boxes, 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, treatment efficacy, the occurrence of adverse events, and discontinuation. Utility estimates were retrieved for both the patient and caregiver. The primary cost inputs included intervention 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. Table 4.2. reports key model inputs, but an exhaustive description of all model inputs and their sources can be found in the Supplement.

Table 4.2. Key Model Inputs

Treatment Effectiveness* on Slowing Disease Progression:	Lecanemab	
MCI due to AD	0.69	
Mild AD	0.69	
Moderate AD	1.00	
Severe AD	1.00	
ARIA:	**Lecanemab**	
Probability of Any ARIA	21.5%	
Probability of Symptomatic ARIA	3.5%	
Probability of AE-Related Discontinuation	6.9%	
Patient Disutilities:	**Community**	**Long-Term Care**
MCI due to AD	-0.17	-0.17
Mild AD	-0.22	-0.19
Moderate AD	-0.36	-0.42
Severe AD	-0.53	-0.59
Caregiver Disutilities:	**Community**	**Long-Term Care**
MCI due to AD	-0.03	-0.03
Mild AD	-0.05	-0.05
Moderate AD	-0.08	-0.08
Severe AD	-0.10	-0.10
Cost Inputs:	**Lecanemab**	
Annual Wholesale Acquisition Cost	$26,500	
MRI Unit Cost	$261	
Annual Cost of Long-term Care	$88,728	

AD: Alzheimer's disease, AE: adverse event, ARIA: amyloid-related imaging abnormalities, MCI: mild cognitive impairment, MRI: magnetic resonance imaging, PET: positron emission tomography
*Only applied to health state progressions (i.e., transitions to more severe health states).

4.3. Results

Base-Case Results

Table 4.3. reports the model outcomes from the health care sector perspective and Table 4.4. reports the model outcomes from the societal perspective. Lecanemab was associated with more costs than the comparator, but also increases in life years, QALYs, evLYs, and years in the community.

Table 4.3. Model Outcomes for the Health Care Sector Perspective

Treatment	Intervention Cost*	Total Cost	Life Years	QALYs	evLYs	Years in the Community
Lecanemab	$109,000	$489,000	6.23	3.84	3.96	4.20
Supportive Care	$0	$363,000	5.77	3.34	3.34	3.69

evLYs: equal-value life years, QALYs: quality-adjusted life years
*Intervention cost doesn't include provider administered mark-up (modeled as 6%), monitoring costs, or administration costs.

The absolute QALYs and evLYs are lower in the societal perspective (Table 4.4.) due to the additional disutility added in this perspective to capture the reduction in quality of life for the caregiver.

Table 4.4. Model Outcomes for the Modified Societal Perspective

Treatment	Intervention Cost*	Total Cost	Life Years	QALYs	evLYs	Years in the Community
Lecanemab	$109,000	$790,000	6.23	3.49	3.64	4.20
Supportive Care	$0	$670,000	5.77	2.98	2.98	3.69

evLYs: equal-value life years, QALYs: quality-adjusted life years

*Intervention cost doesn't include provider administered mark-up (modeled as 6%), monitoring costs, or administration costs.

Table 4.5. reports the incremental cost-effectiveness ratios for the base-case from the health care sector perspective and from the modified societal perspective. The modified societal perspective incremental cost-effectiveness ratios are slightly more favorable than those from the health care sector perspective.

Table 4.5. Base-Case Incremental Cost-Effectiveness Ratios

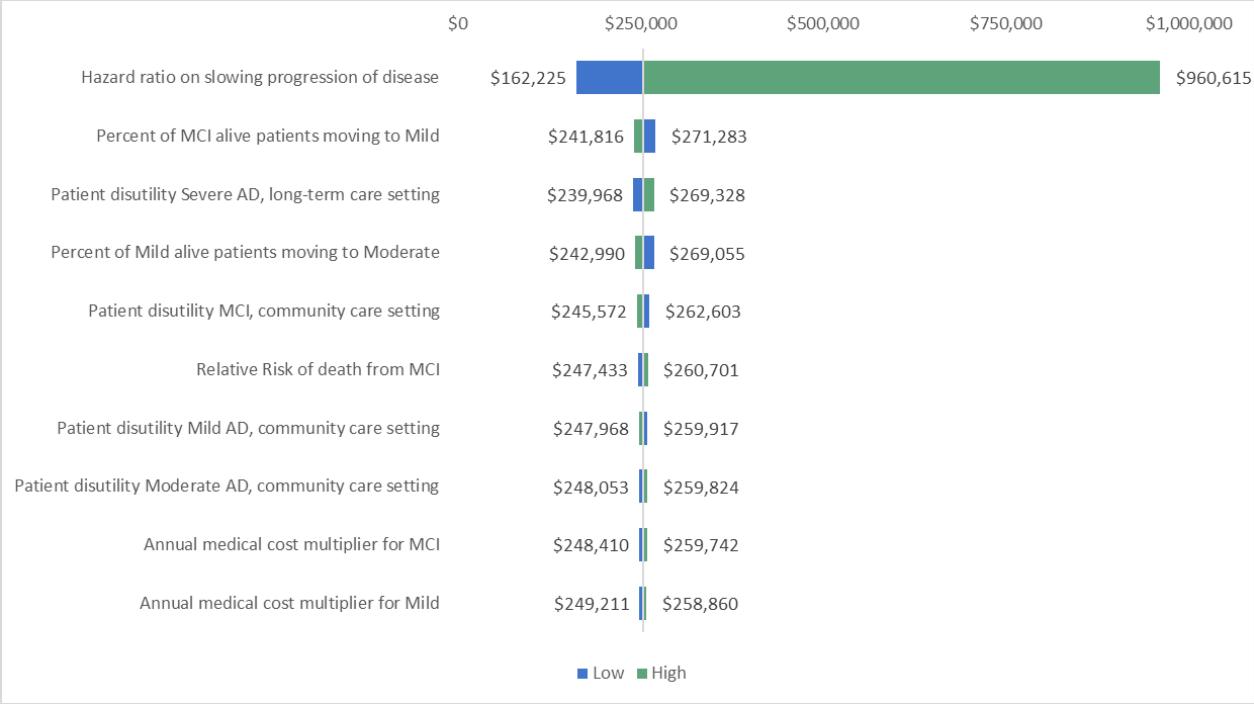
Lecanemab vs. Supportive Care			
Perspective	**Cost per Life Year Gained**	**Cost per QALY Gained**	**Cost per evLY Gained**
Health Care Sector	$277,000	$254,000	$204,000
Societal	$265,000	$236,000	$183,000

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

Sensitivity Analyses

Figure 4.2. displays the tornado diagram from the one-way sensitivity analysis comparing lecanemab in addition to supportive care as compared to supportive care alone. The vertical axis is the incremental cost per QALY gained from the health care sector perspective. The blue coloring represents the range in incremental cost-effectiveness ratios from the base-case estimate to the incremental cost-effectiveness ratio corresponding to the lower bound of that model input. The green coloring represents the range in incremental cost-effectiveness ratios from the base-case estimate to the incremental cost-effectiveness ratio corresponding to the upper bound of that model input. As depicted in the figure, cost-effectiveness is primarily dependent on the effectiveness of the treatment in slowing progression of disease. Table 4.6. reports the lower and upper input, along with their associated incremental cost-effectiveness ratios, for the ten most influential model inputs from the one-way sensitivity analysis.

Figure 4.2. One-Way Sensitivity Analysis Results: Lecanemab versus Supportive Care Alone, Health Care Sector Perspective



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

Table 4.6. Tornado Diagram Inputs: Lecanemab versus Supportive Care Alone, Health Care Sector Perspective

Model Input	Low Input ICER	Upper Input ICER	Lower Input	Upper Input
Hazard Ratio on Slowing Progression of Disease	$162,000	$961,000	0.49	0.92
Percent of MCI Alive Patients Moving to Mild AD	$271,000	$242,000	19%	28%
Patient Disutility Severe AD, Long-Term Care Setting	$240,000	$269,000	-0.71	-0.47
Percent of Mild AD Alive Patients Moving to Moderate AD	$269,000	$243,000	28%	42%
Patient Disutility MCI, Community Care Setting	$263,000	$246,000	-0.20	-0.14
Relative Risk of Death from MCI	$247,000	$261,000	1.48	2.19
Patient Disutility Mild AD, Community Care Setting	$260,000	$248,000	-0.26	-0.18
Patient Disutility Moderate AD, Community Care Setting	$248,000	$260,000	-0.43	-0.29
Annual Medical Cost Multiplier for MCI	$248,000	$260,000	1.00	1.35
Annual Medical Cost Multiplier for Mild AD	$249,000	$259,000	1.27	1.88

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

*Standard error was estimated based on the 95% confidence interval for the primary endpoint of the pivotal trial.

Table 4.7. reports results from the probabilistic sensitivity analysis for lecanemab versus supportive care from the health care sector perspective and the modified societal perspective. Other findings from the probabilistic sensitivity analyses, including credible intervals for lecanemab versus supportive care, can be found in the Supplement.

Table 4.7. Probabilistic Sensitivity Analysis Results: Lecanemab versus Supportive Care

Health Care Sector Perspective	Cost Effective at $50,000	Cost Effective at $100,000	Cost Effective at $150,000	Cost Effective at $200,000
Per QALY Gained	0%	0%	1%	21%
Per evLY Gained	0%	0%	11%	50%
Modified Societal Perspective	**Cost Effective at $50,000**	**Cost Effective at $100,000**	**Cost Effective at $150,000**	**Cost Effective at $200,000**
Per QALY Gained	0%	0%	4%	30%
Per evLY Gained	0%	1%	25%	63%

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

Scenario Analyses

We conducted numerous scenario analyses to test the structural assumptions that were made. Details on the methods and results of each scenario analysis can be found in the Supplement. In Table 4.8, we highlight the findings from the scenario that assumed treatment stopped once a patient reached severe AD with the same assumed treatment effectiveness for moderate AD as

what was modeled in MCI due to AD and mild AD. In this scenario, the incremental clinical outcomes are greater than they were in the base-case because the treatment benefit was assumed to persist through moderate AD, but the treatment costs and non-intervention costs are also greater in this scenario than they were in the base-case.

Table 4.8. Incremental Cost-Effectiveness Ratios Assuming Treatment Continues until Severe AD

Lecanemab vs. Supportive Care			
Perspective	**Cost per Life Year Gained**	**Cost per QALY Gained**	**Cost per evLY Gained**
Health Care Sector	$293,000	$286,000	$226,000
Societal	$290,000	$278,000	$211,000

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

Threshold Analyses

Table 4.9. reports the annual threshold prices for lecanemab from both the health care sector perspective and the modified societal perspective.

Table 4.9. Threshold Analysis* Results for Lecanemab

Health Care Sector Perspective	**Annual Price to Achieve $50,000 Threshold**	**Annual Price to Achieve $100,000 Threshold**	**Annual Price to Achieve $150,000 Threshold**	**Annual Price to Achieve $200,000 Threshold**
Per QALY Gained	$3,200	$8,900	$14,600	$20,300
Per evLY Gained	$4,600	$11,700	$18,800	$26,000
Modified Societal Perspective	**Annual Price to Achieve $50,000 Threshold**	**Annual Price to Achieve $100,000 Threshold**	**Annual Price to Achieve $150,000 Threshold**	**Annual Price to Achieve $200,000 Threshold**
Per QALY Gained	$4,600	$10,500	$16,400	$22,200
Per evLY Gained	$6,300	$13,900	$21,500	$29,100

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

*These threshold prices do not include the provider-administered markup, which was modeled as 6%.

Model Validation

We used several approaches to validate the model. First, we provided the 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 varied model input parameters to evaluate face validity of changes in results. We performed model verification for model calculations using internal reviewers. As part of ICER's efforts in acknowledging modeling transparency, we also shared the model with the relevant manufacturers for external verification shortly after publishing the draft Evidence Report. Finally, we compared results to other cost-effectiveness models in this clinical area.

Uncertainty and Controversies

There are important evidence uncertainties relevant to generating model outcomes, most of which relate to the effectiveness of the treatment on slowing progression of disease. For lecanemab, a hazard ratio on the progression to the next stage of dementia was available, but a confidence interval was not available to fully understand and capture the uncertainty in this estimate. In addition to uncertainty in the effect of each treatment 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 that may change over time and using instruments that might not be sensitive enough to detect AD-specific effects and/or second order effects for the caregivers. Additionally, the utility evidence is from a study that was published more than 20 years ago, so there is a potential that health systems and disease consequences have changed since then. We have conducted extensive sensitivity and scenario analyses, although there may be variation outside of what was modeled.

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 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 these treatments slowing the progression of AD, not stopping the progression or curing the 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.

We do not include aducanumab as an intervention in this cost-effectiveness analysis given the lack of new clinical evidence and the numerous assumptions we included in our prior review. The assumptions we make in the base-case of this review align most closely with the optimistic treatment benefit scenario conducted in our prior AD review, but differences exist in model assumptions and programming between our prior review and this review.

Finally, some commentators have suggested that thresholds should be adjusted for disease severity.[62] 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 an emphasis on results between $100,000-$150,000 per evLYG and QALY gained.

4.4 Summary and Comment

At the current wholesale acquisition cost, lecanemab exceeds commonly cited thresholds. The cost-effectiveness findings are primarily driven by the effectiveness of lecanemab at slowing the progression of disease.

5. Contextual Considerations and Potential Other Benefits

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 table below, 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 short-term risk of death or progression to permanent disability	The acuity of need is high, as AD is a progressive neurodegenerative disease that places a high burden on patients with the disease, caregivers, and society. Currently there is only one FDA-approved disease-modifying therapy.
Magnitude of the lifetime impact on individual patients of the condition being treated	AD has a moderate lifetime impact on patients with the disease. Delaying or stopping progression of AD would improve the quality and, potentially, the length of life of patients. However, late-onset AD affects individuals over the age of 65 and early-onset AD affects only a minority of individuals with the disease. Thus, unlike diseases that impact the patient's entire lifespan, AD has a large effect on a portion of an individual's lifespan, leading to our assessment of moderate lifetime impact.

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 may have left the workforce, delaying progression of the disease may have a significant impact on family life, particularly in patients with early-onset AD.
Caregivers' quality of life and/or ability to achieve major life goals related to education, work, or family life	Delaying progression of AD with anti-amyloid therapy could potentially decrease caregiver impact and stress, increasing caregiver ability to achieve major life goals. Caregivers tend to be younger than patients with AD, and thus the magnitude of benefit to caregivers may be larger over the lifetime than for patients.
Patients' ability to manage and sustain treatment given the complexity of regimen	Current anti-amyloid therapies require monthly or biweekly intravenous infusions, as well as MRIs for monitoring for side effects. This may place a significant burden on patients and caregivers, particularly for those who have difficulty accessing this level of care (e.g., living in a rural area, lack of transportation, caregivers who aren't able to take time off work, etc.), and as the disease progresses.
Health inequities	The impact of lecanemab on health inequities is unclear. Underrepresented minority groups such as Black and Hispanic populations have a higher prevalence of disease and are diagnosed at later stages, thus an effective treatment could potentially 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 are less well represented in clinical trials, and the drugs were not tested in people with moderate or severe AD, thus whether the drug has a differential impact in such populations is not known. In highlighting inequalities in the Alzheimer's disease space, ICER calculated the Health Improvement Distribution Index, looking at the relative proportion of any health gains from treatment of AD for the following groups who have a higher prevalence than the general US population. For more information on how we calculate the Health Improvement Distribution Index, refer to the Supplement. • African American = 1.6

6. Health Benefit Price Benchmarks

Health Benefit Price Benchmarks (HBPBs) for the annual cost of treatment with lecanemab are presented in Table 6.1 below. The HBPB for a drug is defined as the price range that would achieve incremental cost-effectiveness ratios between $100,000 and $150,000 per QALY or per evLY gained. The health benefit price benchmark for lecanemab ranged from $8,900 to $21,500, or a 19% to 66% discount from lecanemab's wholesale acquisition cost.

Table 6.1. Annual Cost-Effectiveness Threshold Prices* for Lecanemab

Health Care Sector Perspective	Annual WAC	Annual Price at $100,000 Threshold	Annual Price at $150,000 Threshold	Discount from WAC to Reach Threshold Prices
QALYs Gained	$26,500	$8,900	$14,600	45%-66%
evLYs Gained	$26,500	$11,700	$18,800	29%-56%
Societal Perspective	**Annual WAC**	**Annual Price at $100,000 Threshold**	**Annual Price at $150,000 Threshold**	**Discount from WAC to Reach Threshold Prices**
QALYs Gained	$26,500	$10,500	$16,400	38%-60%
evLYs Gained	$26,500	$13,900	$21,500	19%-48%

WAC: wholesale acquisition cost, evLY: equal value life year, QALY: quality-adjusted life year

*Threshold prices do not include any provider-administered mark-up, which was assumed to be 6% in the model.

7. Potential Budget Impact

7.1. Overview of Key Assumptions

We used results from the cost-effectiveness model to estimate the potential total budgetary impact of lecanemab for people with MCI due to AD or mild AD. We used the wholesale acquisition cost and the three threshold prices from the health system perspective (at $50,000, $100,000, and $150,000 per QALY) in our estimates of budget impact. The aim of the potential budgetary impact analysis was 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. For 2022-2023, the five-year annualized potential budget impact threshold that should trigger policy actions to manage access and affordability is calculated to be approximately $777 million per year for new drugs.

Potential budget impact was defined as the total differential cost of using each new therapy rather than relevant existing therapies for the treated population, calculated as differential health care costs (including drug costs) minus any offsets in these costs from averted health care events. All costs were undiscounted and estimated over a five-year time horizon.

The budget impact analysis included the estimated number of patients with MCI due to AD or mild AD in the US who would be eligible for treatment with one of these interventions. Using our prior AD report and other analyses, we estimated there are 1.4 million patients in the US eligible for AD treatment that targets beta-amyloid. We assumed that 20% of these 1.4 million patients would initiate treatment in each of the five years, or approximately 280,000 people with AD per year.

We assumed that lecanemab would be added on to standard of care for these individuals and that no current treatments would be displaced by use of the new treatments within the eligible population.

7.2. Results

Figure 7.1. illustrates the health care sector perspective cumulative per-patient budget impact calculations for lecanemab compared to supportive care, based on the annualized wholesale acquisition cost of $26,500 per year of treatment. The average potential budgetary impact for lecanemab was approximately $27,000 per patient in year one, with the cumulative net cost increasing in years two through five as treatment continues, reaching approximately $104,000 by the end of the five-year horizon. The annual net cost slowly declined each year given various factors including treatment discontinuation and cost offsets.

Figure 7.1. Cumulative Per-Patient Budget Impact of Lecanemab

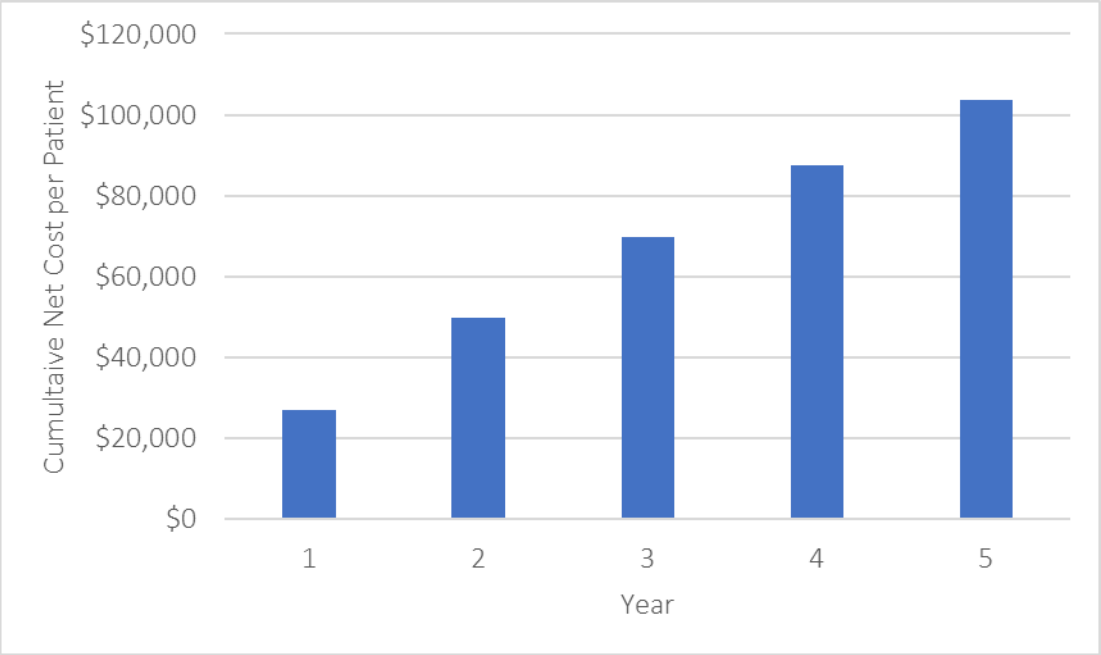
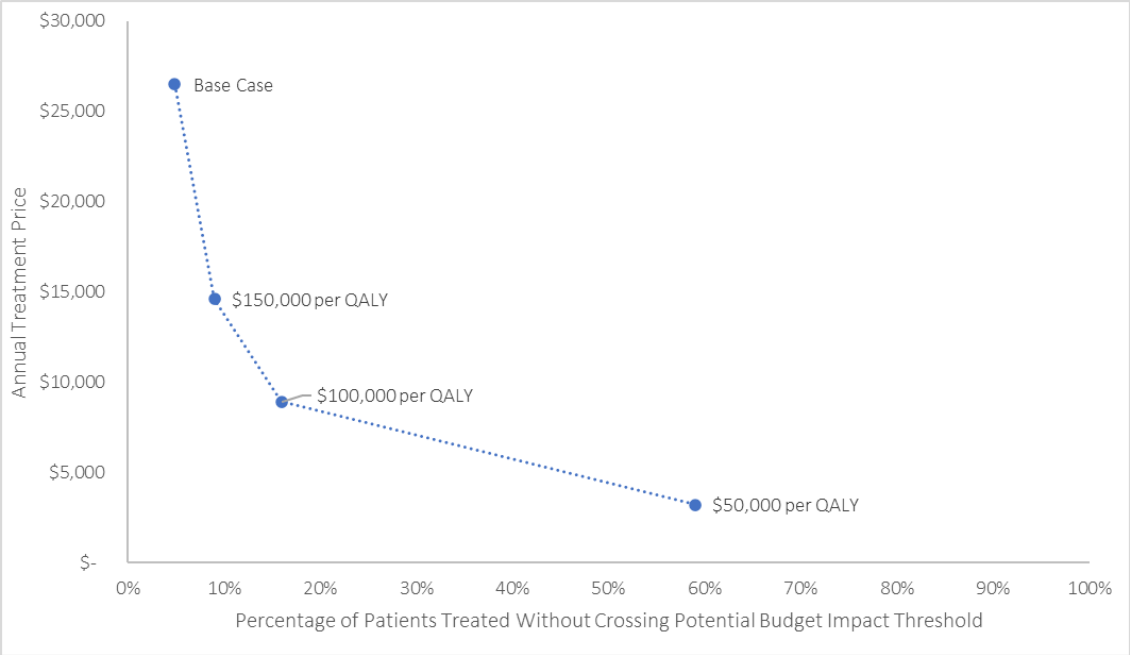


Figure 7.2 illustrates the heath care sector perspective potential budget impact of lecanemab treatment, based on the annualized wholesale acquisition cost ($26,500 per year of treatment), and the health care sector threshold prices to reach $50,000, $100,000, and $150,000 per QALY. Approximately 5% of the roughly 280,000 patients could be treated without crossing the ICER potential budget impact threshold of $777 million per year over five years at the annualized wholesale acquisition cost of $26,500 per year. Approximately 9% of patients could be treated each year without crossing the budget impact threshold at the $150,000 per QALY threshold price, increasing to approximately 16% of the population at the $100,000 per QALY threshold price, and increasing to approximately 59% of the population at the $50,000 per QALY threshold price.

Figure 7.2. Potential Budgetary Impact of Lecanemab Treatment



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Supplemental Materials

A. Background: Supplemental Information

A1. Definitions

General definitions

Alzheimer's disease (AD): A neurodegenerative brain disease with presenting symptoms including impairment in cognition (memory, language, executive function (e.g., problem-solving and completing tasks), and visuospatial function, all of which result in the loss of ability to perform activities of daily living (e.g., paying bills, bathing, dressing, etc.).[63,64] Changes in mood and personality, along with decreased or poor judgment and sleep disturbances, also occur. 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. Stages of AD include a preclinical phase, MCI due to AD, and dementia due to AD.[2]

Amyloid-related imaging abnormalities (ARIA): Abnormalities on MRI that can present as either edema/effusion (ARIA-E) or hemorrhage or superficial siderosis (ARIA-H), and is commonly associated with anti-amyloid therapies. ARIA may be asymptomatic (observed only on neuroimaging) or can cause symptoms such as headache, nausea, confusion, and gait abnormalities. ARIA is most commonly seen early on in a treatment period and is more frequently observed in ApoE ε4 carriers as compared to non-carriers. Management of ARIA may include MRI monitoring, dose suspension or termination, treatment titration, etc.[65]

- **Hemorrhage:** Bleeding from a damaged blood vessel.
- **Superficial siderosis:** A degenerative disorder affecting the brain and spinal cord. It is the result of persistent long-term bleeding into the subarachnoid space in the brain resulting in a build-up of hemosiderin on the brain surface and pia matter from cerebrospinal fluid.[66] Symptoms include hearing loss, movement abnormalities, and motor difficulties.

Apolipoprotein ε4 (ApoE ε4): An allele that increases the risk of an individual developing AD. Up to 25% of Caucasian individuals are heterozygous (carry one copy) of the ε4 allele, which increases the risk of developing AD by 3-fold.[67] 2% of the population are homozygous (carry two copies) of the ε4 allele, and have a 15-fold risk of developing AD compared with the general population. More research is recommended by the Alzheimer's Association to better understand the correlation between ApoE ε4 carriers and the onset of AD.[2]

Disease-modifying therapy: Treatments or interventions that affect the underlying pathophysiology of a disease and have a beneficial outcome on the course of AD.[68]

Biomarkers

Amyloid plaque: Extracellular deposits of the amyloid beta protein mainly in the grey matter of the brain.

Beta-amyloid: Beta-amyloid (Aβ) plays a key role in the pathogenesis of Alzheimer's disease and can be imaged in vivo using florbetaben, florbetapir, or flutemetamol PET tracers. Beta-amyloid is formed from the breakdown of an amyloid precursor protein. Beta-amyloid refers to peptides of 36-43 amino acids that are the main component of amyloid plaques. Aβ monomers, a disordered peptide, can aggregate into various forms, including oligomers (soluble), protofibrils and amyloid fibrils (insoluble).[69] Different Alzheimer's disease therapies aim to target different species of amyloid. Amyloid plaques contain both Aβ40 and Aβ42. **Aβ1-42 and Aβ1-40** are biomarkers in Alzheimer's disease detected in plasma or cerebrospinal fluid, with higher values representing more amyloid. Aβ1-42 is considered to be important for progression as it is more toxic. **Aβ42/40** is also a biomarker for early detection of amyloid pathology. A lower ratio is indicative of elevated amyloid.

Tau protein: A microtubule-associated protein that form insoluble filaments that accumulate as neurofibrillary tangles in Alzheimer's disease.[70] Tau is suggested to help stabilize neurons in the brain and a buildup of tau impacts the function of brain cells. Tau increases with age and has been suggested to be a general marker of neurodegeneration.[71] Tau is important in Alzheimer's disease as models suggest that while amyloid PET may be the earliest detected abnormal biomarker, it is followed closely by CSF tau.[72] Total-tau (t-tau) is used as a key biomarker in Alzheimer's disease research.

Flortaucipir: The most widely studied tau-specific radiotracer and is specific to the tau aggregates of AD.

Phosphorylated tau (P-tau): Phosphorylated tau are tau in an abnormally hyperphosphorylated state. A buildup of p-tau leads to synaptic impairment and neurofibrillary tangles.[73] P-tau has been considered a more specific marker for Alzheimer's disease as neurofibrillary tangles consist of tau protein in this state.

Neurogranin: Calmodulin-binding protein expressed primarily in the brain, particularly in dendritic spines, and participating in the protein kinase C signaling pathway. Neurogranin is considered a biomarker for Alzheimer's disease.

Plasma: The liquid component of the blood that is necessary to distribute nutrients, remove waste, and prevent infection. Plasma samples are taken in Alzheimer's disease research to examine biomarkers such as tau, p-tau, and beta-amyloid.

Cerebrospinal fluid (CSF): Body fluid found in the tissue that surrounds the brain and spinal cord, providing a cushion from injury and providing nutrients to the brain. CSF samples are taken in Alzheimer's disease research to examine biomarkers such as tau, p-tau, and beta-amyloid.

Positron Emission Tomography (PET) scan: A minimally-invasive functional imaging technique that uses radioactive substances (radiotracers) to visualize and measure changes in activity in organs and tissues. PET scans are used for diagnosing Alzheimer's disease by measuring the build-up of beta-amyloid in the brain. Amyloid PET is a specific type of PET scan where a ligand that binds to amyloid plaque is labeled with a radioisotope (e.g., 11C, 13N, 150, 18F) to visualize and measure amyloid.

- **Standardized uptake value ratio (SUVr)**: A widely used PET quantifier. This is a method of determining activity in PET imaging and is used as a measure for quantifying the global Aβ and tau burden.

- **Centiloids:** Standardized measure of amyloid PET imaging that scales the outcome of each analysis method or tracer to a 0 to 100 scale. The units of this scale have been named "Centiloids." SUVr can be transformed into centiloids by using individual-level data from cognitive controls and "typical" individuals with AD as anchors.

Magnetic resonance imaging (MRI): Medical imaging technique used to create images of organs and tissues in the body. MRIs are used in Alzheimer's disease research to detect brain abnormalities for diagnosis and in clinical trials to monitor ARIA.

- **Hippocampal volume**: Hippocampus is a brain structure embedded in the temporal lobe that has a major role in learning and memory. Large hippocampal volume is positively associated with memory performance.

- **Whole brain volume**: Collective volume of the entire brain in structural imaging, without considering regionally specific differences in the volume of any individual structures. In Alzheimer's disease, as connections between networks of neurons break down then brain regions begin to shrink.

- **Ventricular volume**: Ventricles are one of a system of four communicating cavities within the brain and are filled with cerebrospinal fluid. Enlarged ventricles have been associated with decreases in cognitive functioning.

Key Outcome Instruments

Cognitive Outcomes

Clinical Dementia Rating – Sum of Boxes (CDR-SB) is a structured interview 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.[27] Higher scores suggest greater disease severity with scores between 0.5-4.0 indicating questionable cognitive impairment, 4.5-9 mild dementia, 9.5-15.5 indicating moderate dementia, and 16.0-18.0 indicating severe dementia. Minimal Clinically Important Difference (MCID) has been defined as a change of 0.98-1.63 for MCI due to AD and mild AD dementia.[36]

Alzheimer's Disease Assessment Scale – Cognitive Subscale (ADAS-Cog) is an objective neurological assessment that examines the severity of cognitive and non-cognitive function from mild to severe AD. Only the cognitive subscale (ADAS-Cog) was used which includes 11 subject-completed tests and observer-based assessments of memory, language, and praxis. ADAS-Cog14 includes all 11 items plus a test of delayed word recall, number cancellation task, and a maze task with a score ranging from 0-90 with higher scores reflecting greater impairment. MCID has been defined as a change of 2 points for MCI due to AD[37] and ≥3 points for mild AD.[38,39]

Alzheimer's Disease Cooperative Study – Activities of Daily Living Inventory (MCI version) (ADCS-MCI-ADL) is a caregiver completed scale that measures basic and instrumental abilities. The MCI version has been adapted for individuals with mild cognitive impairment[74] and includes 18 items with total scores ranging from 0-53, with lower scores representing poorer functioning. There is no data on MCID.

AD Composite Score (ADCOMS) is a weighted score that includes the MMSE (2 items: Constructional praxis and orientation time), CDR-SB (6 items: personal care, home and hobbies, community affairs, judgment and problem solving, orientation, and memory), and ADAS-Cog14 (4 items: word finding difficulty, word recognition, orientation, and delayed word recall).[75] Total scores range from 0-1.97. A score of <0.29 is indicative of normal cognition, 0.29 to <0.50 is indicative of MCI, 0.50 to 0.80 is indicative of mild AD, and >0.80 is indicative of at least moderate AD. There is no data on MCID.

Quality of Life Outcomes

European Quality of Life – 5 dimensions (5 level version) (EQ-5D-5L): A self-reported visual analog scale that covers dimensions of health such as mobility, self-care, activities, pain, and anxiety/depression.[76]

Quality of Life in Alzheimer's Disease (QOL-AD): A patient-reported (or caregiver reported, e.g., subject by proxy) questionnaire reporting on quality of life in those with Alzheimer's disease.[77]

Zarit Burden Interview: An instrument used to measure stress experienced by caregivers of those with Alzheimer's disease.[78]

Other Relevant Definitions

Health Improvement Distribution Index: The Health Improvement Distribution Index identifies a subpopulation that has a higher prevalence of the disease of interest and therefore, creates an opportunity for proportionately more health gains within the subpopulation. This opportunity may be realized by achieving equal access both within and outside the identified subpopulation to an intervention that is known to improve health. The Health Improvement Distribution Index is defined as the disease prevalence in the subpopulation divided by the disease prevalence in the overall population. For example, if the disease prevalence was 10% in poor Americans whereas the disease prevalence across all Americans was 4%, then the Health Improvement Distribution Index would be 10%/4% = 2.5. For interventions known to increase health in this disease and that accomplish equal access across the entire population, poor Americans would receive 2.5 times the health improvements as compared to the same sized group of Americans without regard to economic status. Health Improvement Distribution Indexes above 1 suggest that more health may be gained on the relative scale in the subpopulation of interest when compared to the population as a whole. This statistic may be helpful in characterizing a treatment's contextual considerations and potential other benefits (Section 5). For the calculation for the HIDI for African Americans, we used population estimates of clinical AD calculated by Rajan et al., which were based on the Chicago Health and Aging Project and adjusted based on the 2020 US census.[79] The overall 2020 US census adjusted prevalence of clinical AD was 11.3%.

- African American = 18.6%/11.3% = 1.6

A2. Potential Cost-Saving Measures in Alzheimer's Disease

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://icer.org/our-approach/methods-process/value-assessment-framework/). These services are ones that would not be directly affected by beta-amyloid therapies for AD (e.g., skilled nursing care), as these services will be captured in the economic model. Rather, we are seeking services used in the current management of mild cognitive impairment or mild 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 people with Alzheimer's disease that could be reduced, eliminated, or made more efficient. We received a suggestion that repeating neuropsychological testing to monitor cognitive decline may not be necessary.

B. Patient Perspectives: Supplemental Information

B1. Methods

ICER engaged with people with AD and caregivers, 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 nine persons with AD, six caregivers, two advocacy organizations, nine clinical experts, one payer, and four manufacturers via conference calls 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 people with AD and caregivers provided to us by patient organizations.[4,80]

People living with AD, caregivers, and advocacy groups provided information on the impact of AD on individuals with the disease and caregivers throughout the disease course, particularly concerning aspects of the disease and caregiving that are not well-reflected in the current literature, and their thoughts about current and future treatment options. These informal interviews provided important information to help raise issues important to persons with Alzheimer's and their caregivers; it is important to note that the interviews were not meant to represent a formal study of patient and caregiver perspectives. Patient advocacy organizations also assisted with literature review to find information that was considered for inputs into the economic model.

We spoke with a wide range of people living with AD, mainly people over the age of 50 with mild or moderate AD and mostly living at home. We spoke with both men and women, as well as both White and African American people living with AD. The caregivers we spoke with represented a wide variety of ages (from 30 to above 70) and caregiving experience, caring for loved ones across the disease spectrum (mild to severe) and in various settings (home and long-term care). We spoke with both male and female, and White, Black, and Hispanic caregivers.

Clinical experts were chosen based on their expertise in diagnosing, treating, and/or researching AD, as well as recommendations from other stakeholders. We spoke with neurologists and geriatricians with expertise treating people with AD, as well as epidemiologists and clinical researchers. Clinical experts also believe that the main goal of treatment for AD is to maintain independence, and that disease-modifying drugs would be a welcome addition to the treatment arsenal. However, because there have been multiple purported disease-modifying drugs that have previously failed during the clinical trial phase, they are cautious and feel they need clear evidence

demonstrating such an effect from a new therapy. Additionally, clinical experts also cited issues with clinical trial outcome measures, including that CDR-SB may not be sufficiently sensitive to changes in cognition and function.

Payers were concerned about the use of surrogate markers as endpoints in clinical trials, and the lack of clear association between those surrogate markers and clinical outcomes.

Manufacturers noted the urgency of developing new treatments for AD, the disproportionate impact of AD on persons of color and their caregivers, and that better information on the impact of AD treatments on quality of life for both individuals with the disease and caregivers is needed.

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 individuals 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 people with AD, such as pain, falls, and incontinence.

American Psychiatric Association[81]

The American Psychiatric Association published practice guidelines for the treatment of individuals 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[63,64,82]

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[82]. 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 people with the disease in the AD continuum.

Aducanumab: Appropriate Use Recommendations[83]

After FDA approval of aducanumab, a panel of Alzheimer's disease experts convened to discuss best practices for aducanumab use. The panel defined the appropriate patient population for initiation of treatment, which includes individuals with early AD with positive amyloid via PET scan or CSF investigation, and recommends potential exclusion criteria, including concomitant use of anticoagulation. The expert panel also recommend an MRI monitoring schedule of baseline and surveillance MRIs based on aducanumab titration, and management strategies for ARIA, including MRI monitoring intervals and recommendations for dosing. Finally, the expert panel made recommendations on the healthcare system resources needed for safe and appropriate use of aducanumab, such as clinical expertise, access to testing for amyloid, infusion resources, access to MRI, and access to family and patient education and support.

D. Comparative Clinical Effectiveness: Supplemental Information

D1. Detailed Methods

A prior version of this report included a review of donanemab. Due to the manufacturer receiving a Complete Response Letter from the US Food and Drug Administration (FDA) on January 19, 2023 for donanemab's accelerated approval biologics license application, we have removed it from this version. There was no new clinical evidence for aducanumab since the previous August 2021 review[8] that would have affected our assessment and thus aducanumab was not reviewed in this report.

PICOTS

Population

The population of focus for the review was adults with early AD (i.e., MCI due to AD [also termed "prodromal" Alzheimer's] and mild AD dementia) with evidence of AD pathology (e.g., amyloid positivity). This population approximates individuals whose condition would be categorized as Stages 3 or 4 using diagnostic criteria outlined by the FDA.[84] Evidence that includes individuals with AD in Stage 2 will only be considered if the sample also includes individuals in Stage 3.

Interventions

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

Comparators

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

Outcomes

The outcomes of interest are described in the list below.

- Patient-centered Outcomes
    - Change in:
        - Ability to maintain independence and autonomy
        - Ability to perform activities of daily living (e.g., as measured by AD Cooperative Study-Activities of Daily Living Inventory-MCI, etc.)
        - Cognitive function (e.g., as measured by Clinical Dementia Rating, Mini-Mental State Examination, AD Composite Score, Alzheimer's Disease Assessment Scale – Cognitive Subscale, Integrated Alzheimer's Disease Rating Scale, Montreal Cognitive Assessment Test, etc.)
        - Neuropsychiatric symptoms (e.g., as measured by Neuropsychiatric Inventory Questionnaire)
    - Delayed entry into institutional care
    - Disease progression
    - Symptom progression
    - Maintenance of identity and personality
    - Quality of life
    - Emotional wellbeing
    - Caregiver impact
        - Caregiver quality of life
        - Caregiver health
        - Caregiver productivity
    - Behavioral change
    - Ability to communicate
    - Adverse events including but not limited to
        - Serious adverse events
        - Discontinuation due to adverse events
        - Infusion-related reactions
        - Death
        - Symptomatic amyloid-related imaging abnormalities (ARIA-E and ARIA-H)
- Other Outcomes
    - Level of beta-amyloid (e.g., PET, CSF)
        - Percentage of amyloid
            - Percentage reduction
            - Absolute percentage
        - Amyloid clearance
            - Mean reduction in amyloid from baseline

        - Percentage of participants reaching amyloid negativity
        - Rapidity of participants reaching amyloid negativity
    - Durability of biomarker reductions (e.g., tau levels and beta-amyloid)
- Level of tau proteins (e.g., CSF phosphorylated tau, total tau, PET ligand)
- Neuroinflammation
- Brain atrophy
- Brain volume (e.g., hippocampal volume, ventricular volume, or whole brain volume)
- Additional biomarkers may be reviewed based on input from manufacturers and clinical experts as the review progresses

Timing

Evidence on intervention effectiveness and evidence on harms were derived from studies of any duration.

Settings

Evidence from all relevant settings was 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.

		Checklist Items
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.
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 donanemab, lecanemab, and updated evidence for aducanumab, in addition to supportive care, for the treatment of early Alzheimer's disease (AD), i.e., MCI due to AD and mild AD dementia followed established best research methods.[85,86] We conducted the review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[87] The PRISMA guidelines include a checklist of 27 items, which are described further in Table D1.

We searched MEDLINE, EMBASE, Cochrane Database of Systematic Reviews, and Cochrane Central Register of Controlled Trials 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. 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. At the time of the updated search (02/02/2023), lecanemab had been given a brand name (Leqembi) and, for completeness, this search term was included in the updated search.

To supplement the database searches, we performed a manual check of the reference lists of included trials and reviews and invite 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, and 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/). Where feasible and deemed necessary, we also accepted data submitted by manufacturers "in-confidence," in accordance with ICER's published guidelines on acceptance and use of such data (https://icer.org/guidelines-on-icers-acceptance-and-use-of-in-confidence-data-from-manufacturers-of-pharmaceuticals-devices-and-other-health-interventions/).

Table D1.1. Search Strategy of Medline 1996 to Present with Daily Update and Cochrane Central Register of Controlled Trials (lecanemab and donanemab)

1	(lecanemab or 'ban 2401' or ban2401 or Leqembi).ti,ab.
2	(donanemab or 'ly 3002813' or ly3002813).ti,ab.
3	1 or 2
4	(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 video audio media).pt.
5	3 not 4
6	(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.)
7	5 not 6
8	Limit 7 to English Language
	Remove duplicates from 8

Table D1.2. Search Strategy of EMBASE SEARCH (lecanemab and donanemab)

#1	lecanemab/exp
#2	(lecanemab OR "ban 2401" OR ban2401 OR Leqembi):ti,ab
#3	#1 OR #2
#4	donanemab/exp
#5	(donanemab OR "ly 3002813" OR ly3002813):ti,ab
#6	#4 OR #5
#7	#3 OR #6
#8	('case report'/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 'short survey'/it)
#9	#7 NOT #8
#10	('animal'/exp OR 'nonhuman'/exp OR 'animal experiment'/exp) NOT 'human'/exp
#11	#9 NOT #10
#12	#11 AND [english]/lim

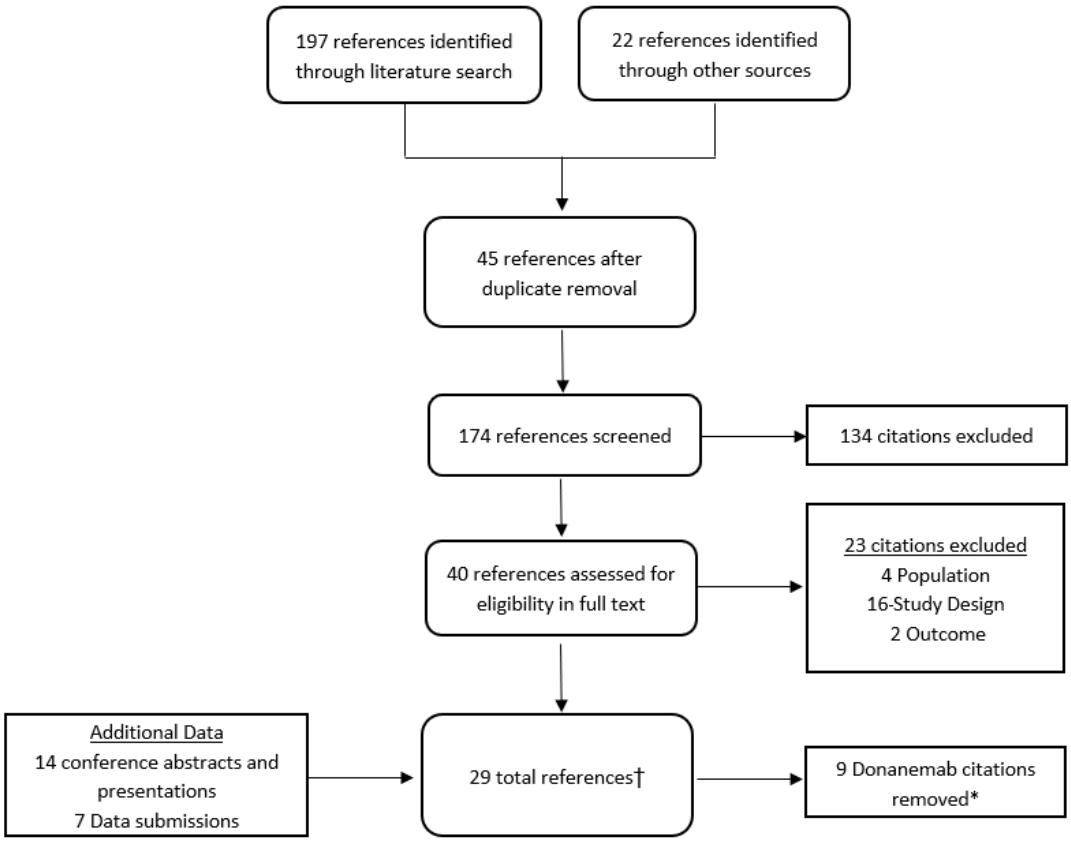
Table D1.3. Search Strategy of Medline 1996 to Present with Daily Update and Cochrane Central Register of Controlled Trials (updated evidence for aducanumab)

1	(aducanumab or BIIB037 or 'BIIB 037' or BIIB-037 or BIIB37 or BIIB-37 or aduhelm).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
8	Limit 7 to yr=”2020 -Current”

Table D1.4. Search Strategy of EMBASE SEARCH (updated evidence 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 OR aduhelm: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
#8	#7 AND [18/05/2021]/sd

Figure D1. PRISMA flow Chart Showing Results of Literature Search for Aducanumab, Lecanemab and Donanemab for Alzheimer's Disease.



*At the time of our revised report, donanemab had been removed as an intervention from this report. Thus, nine references that provided data on donanemab were removed.
†Our search did not identify any new aducanumab references. Thus, aducanumab was not included in our review.

Study Selection

We performed screening at both the abstract and full-text level. A single investigator screened all abstracts identified through electronic searches according to the inclusion and exclusion criteria described earlier. We did not exclude any study at abstract-level screening due to insufficient information. For example, an abstract that did not report an outcome of interest would be accepted for further review in full text. We retrieved the citations that were accepted during abstract-level screening for full text appraisal. One investigator reviewed full papers and provided justification for exclusion of each excluded study.

Data Extraction

Data were extracted into Microsoft Excel. The basic design and elements of the extraction forms followed those used for other ICER reports. Elements included a description of patient populations, sample size, duration of follow-up, funding source, study design features, interventions (agent, dosage, frequency, schedules), concomitant therapy allowed and used (agent, dosage, frequency, schedules), outcome assessments, results, and risk of bias for each study. The data extraction was performed in the following steps:

1. One reviewer extracted information from the full articles, and a second reviewer validated the extracted data.

2. Extracted data were reviewed for logic, and a random proportion of data were validated by a third investigator for additional quality assurance.

Risk of Bias Assessment

We examined the risk of bias for each randomized control trial in this review using criteria published in the Cochrane Risk of Bias Assessment Tool Version 2.[88,89] Risk of bias was assessed by study outcome for each of the following aspects of the trials: randomization process, deviation from the intended interventions, missing outcome data, measurement of the outcome, selection of the reported results, and overall risk of bias. Two reviewers independently assessed these domains. Any disagreements were resolved through discussion or by consulting a third reviewer. We did not assess the risk of bias in trials where we only had access to conference abstracts/presentations.

To assess the risk of bias in trials, we rated the categories as: "low risk of bias", "some concerns", or "high risk of bias". Guidance for risk of bias ratings using these criteria is presented below:

Low risk of bias*: The study is judged to be at low risk of bias for all domains for this result.*

Some concerns*: The study is judged to raise some concerns in at least one domain for this result, but not to be at high risk of bias for any domain.*

High risk of bias*: The study is judged to be at high risk of bias in at least one domain for this result* or *the study is judged to have some concerns for multiple domains in a way that substantially lowers confidence in the result.*

We examined the risk of bias for the following outcomes: CDR-SB, ADAS-Cog14, ADCS-MCI-ADL, and ARIA. See Table D1.5.

Table D1.5. Risk of Bias Assessments

Trial name	Randomization Process	Deviation from the Intended Interventions	Missing Outcome Data	Measurement of the Outcome	Selection of the Reported Result	Overall Risk of Bias
CDR-SB						
CLARITY AD [35]	Low	Low	Low	Some concerns	Low	**Low**
ADAS-Cog14						
CLARITY AD [35]	Low	Some concerns	Low	Low	Low	**Some concerns**
ADCS-MCI-ADL						
CLARITY AD [35]	Low	Low	Low	Some concerns	Low	**Some concerns**
ARIA						
CLARITY AD [35]	Low	Low	Low	High	Low	**High**

Note: All "some concerns" or "high risk" favored the experimental group.

ADAS-Cog14: Alzheimer's Disease Assessment Scale – Cognitive Subscale, ADCS-MCI-ADL: Alzheimer's Disease Cooperative Study – Activities of Daily Living Inventory (MCI version), ARIA: Amyloid-related imaging abnormalities, CDR-SB: Clinical Dementia Rating – Sum of Boxes

Evaluation of Clinical Trial Diversity

We evaluated the demographic diversity of clinical trials using the ICER-Developed Clinical Trial Diversity Rating Tool. The tool is designed to evaluate the three demographic characteristics described in Table D1.6. below. Additional guidance on using the tool is described below.

Table D1.6. Demographic Characteristics and Categories

Demographic Characteristics	Categories
1. Race and Ethnicity	Racial categories: • White • Black or African American • Asian • American Indian and Alaskan Native • Native Hawaiian and Other Pacific Islanders Ethnic Category: • Hispanic or Latino
2. Sex	• Female • Male
3. Age	• Older adults (≥65 years)

Rating Guide

Representation for each demographic category is evaluated relative to the disease prevalence, using the metric "Participant to Disease-prevalence Representation Ratio" (PDRR). Next, a representation score is assigned based on the PDRR estimate. The score for each demographic category ranges from 0 to 3 based on the PDRR cut points presented in Table D1.7. Finally, based on the total score of the demographic characteristics (e.g., race and ethnicity), the categories "good," "fair," or "poor" are used to communicate the overall level of diversity of a clinical trial. The description of the rating categories for each demographic characteristic is provided in Table D1.8. A second diversity rating that evaluates the subpopulation of patients recruited from the US is provided for multinational trials.

Table D1.7. Representation Score

PDRR	Score
0 or Information on Demographic Category Not Reported	0
>0 and Less Than 0.5	1
0.5 to 0.8	2
≥0.8	3

PDRR: Participant to Disease-prevalence Representation Ratio

Table D1.8. Rating Categories

Demographic Characteristics	Demographic Categories	Maximum Score	Rating Categories (Total Score)
Race and Ethnicity*	Asian, Black, White, and Hispanic	12	Good (11-12) Fair (7-10) Poor (≤6)
Sex	Male and Female	6	Good (6) Fair (5) Poor (≤4)
Age	Older adults (≥65 years)	3	Good (3) Fair (2) Poor (≤1)

*American Indian or Alaskan Native & Native Hawaiian or Other Pacific Islander are not factored into the overall racial and diversity rating. However, information on enrollment and PDRR estimates are reported when reliable prevalence estimates are available.

Results

Table D1.9. Race and Ethnicity

	White	Black	Asian	Hispanic	Total score	Diversity Rating	AIAN	NHPI
Prevalence	72.10%	16.97%	4.55%	20.71%			1.09%	NR
G000-201	NR	NR	NR	NR	--	--	NR	NR
PDRR	NC	NC	NC	NC	--	--	NC	NC
Score	0	0	0	0	0	Poor	--	--
CLARITY AD	76.90%	2.60%	16.90%	12.90%	--	--	0.11%	0.06%
PDRR	1.07	0.15	3.71	0.6	--	--	0.10	NE
Score	3	1	3	2	9	Fair	--	--

AIAN: American Indian or Alaskan Native, NR: Not Reported, NC: Not Calculated, NE: Not Estimated, NHPI: Native Hawaiian or Pacific Islander, PDRR: Participant to Disease-prevalence Representation Ratio

Table D1.10. Race and Ethnicity in US Participants Only

	White	Black	Asian	Hispanic	Total score	Diversity Rating	AIAN	NHPI
Prevalence	72.10%	16.97%	4.55%	20.71%			1.09%	NR
G000-201	NR	NR	NR	NR	--	--	NR	NR
PDRR	NC	NC	NC	NC	--	--	NC	NC
Score	--	--	--	--	--	--	--	--
CLARITY AD	94.80%	4.40%	0.80%*	21.90%	--	--	NR	NR
PDRR	1.31	0.26	0.18	1.06	--	--	NC	NC
Score	3	1	1	3	8	Fair	--	--

AIAN: American Indian or Alaskan Native, NR: Not Reported, NC: Not Calculated, NHPI: Native Hawaiian or Pacific Islander, PDRR: Participant to Disease-prevalence Representation Ratio

*We estimated the number of Asian participants in the US based on the subgroup analyses of US participants reported in the van Dyck et al. (2022) manuscript. However, these participants likely included those who were AIAN or NHPI; thus, the number of Asian participants was likely lower than our estimation.

Table D1.11. Sex and Age

	Sex				Age		
	Male	Female	Score	Rating	Older Adults (≥65 years)	Score	Rating
Prevalence	38.40%	61.60%			NR		
G000-201	50.4%	49.60%	--	--	--	--	--
PDRR	1.31	0.81	--	--	NC	--	--
Score	3	3	6	Good	--	NC	NC
CLARITY AD	47.70%	52.30%	--	--	--	--	--
PDRR	1.24	0.85	--	--	NC	--	--
Score	3	3	6	Good	--	NC	NC

NC: Not Calculated, PDRR: Participant to Disease-prevalence Representation Ratio

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 (see Appendix D).[90,91]

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 these newer treatments, we scanned the ClinicalTrials.gov site to identify studies completed more than two years ago. Search terms included lecanemab, ban2401, donanemab, ly3002813, aducanumab, aduhelm, and biib037. We selected studies which would have met our inclusion criteria, and for which no findings have been published. We will provide 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

The studies were summarized in the text and in evidence tables of the Evidence Report. This summary is key to understanding the evidence base pertaining to the topic. Any 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 was noted in text of the report.

D2. Additional Clinical Evidence

Lecanemab

CLARITY AD

Methods

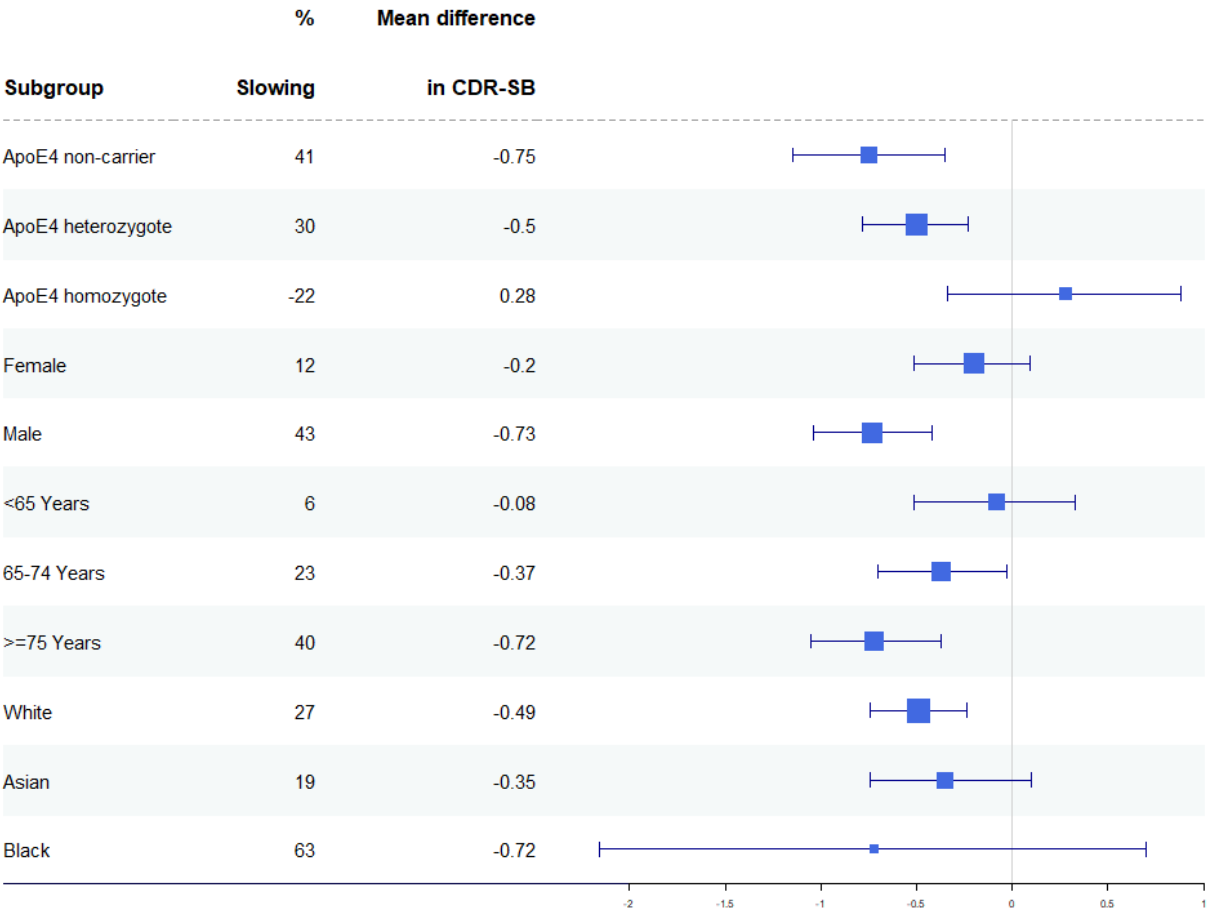
The inclusion criteria for CLARITY AD were participants aged between 50 and 90 years, had a mild cognitive impairment due to Alzheimer's disease or mild Alzheimer's disease dementia, objective impairment in episodic memory, amyloid positive as determined by PET or CSF (Aβ1–42), had Mini-Mental State Exam (MMSE) score of 22-30, BMI 17-35, and, if they were receiving any treatment for AD symptoms, were on a stable dose for 12 weeks prior to baseline. Participants were excluded if they had any other neurological condition that may be contributing to cognitive impairment, any psychiatric diagnosis/symptoms, Geriatric Depression Scale (GDS) score ≥8, contraindications to MRI, or lesions on MRI that could indicate dementia diagnosis other than Alzheimer's disease. Full inclusion and exclusion criteria are described in Table D3.1. in the Supplement. During the trial, an amendment was made to the information sheet to highlight the risk of brain bleeding.[46]

Additional Results

Cognitive Outcomes

Prespecified subgroup analyses were conducted on the cognitive outcomes. In the main report, we described four subgroups that were consistent across the four cognitive outcomes. In this supplement, we also present the race (global) subgroup. Black participants showed a greater slowing of decline compared to White and Asian participants. See Figure D2. A greater slowing of decline in Black participants was also seen in ADCOMS and ADCS-MCI-ADL. See Supplement Tables D3.20-21. However, this group consisted of 44 individuals and thus should be interpreted with caution.

Figure D2. Forest Plot of Subgroup Analyses for CDR-SB at 18 Months (Age, ApoE ε4 Genotype, Sex, and Race)



Beta-amyloid Levels

Changes in beta-amyloid are described in the main report. Changes in plasma Aβ42/40 ratio and CSF values (Aβ1-42 and Aβ1-40) are described in this supplement. For participants who consented to the CSF substudy, CSF samples were taken at baseline, week 53, and week 77, and plasma samples were taken at baseline, week 53, and week 79. Based on an analysis with 73.3% of the total participants (N=1316), plasma Aβ42/40 ratio increased more in the lecanemab group (0.008), compared to the placebo group which remained constant (0.001). Based on an analysis with 11% of the total participants (N=198) participants, there was an increase in CSF Aβ1–42 in the lecanemab group (281.8), compared to a very slight decrease in the placebo group (-6.5). Based on an analysis with 7.9% of the total participants (N=142), there was a decrease in CSF Aβ1-40 in the lecanemab group (-417.9), compared to a decrease in the placebo group (-89.9).[42] The investigators noted that these findings suggest sustained amyloid reversal effects.

Brain volume was assessed using MRI. MRI scans were taken at screening and week 9, 13, 27, 53, and 79 (or at early termination visit). Volumetric MRI data was available for approximately 75% of participants in the CLARITY AD trial at 18 months, and showed increased atrophy in the whole brain and cortical thickness, and decreased atrophy in the hippocampus. Data was digitized from the figures presented at the Clinical Trials on Alzheimer's Disease (CTAD) 2022 conference[42] and are reported in Supplement Table D3.4.

Biomarkers

T-tau was examined in 199 participants consenting to the tau substudy. Tau was examined by CSF at baseline, week 53, and week 77 and, in those consenting to the PET substudy, via PET at baseline, week 59, and week 79. There was a significant decline in CSF tau in the lecanemab group, compared to an increase in the placebo group (-29.1 vs 95.3, p<0.001).[35] Subgroup analysis conducted examining changes in tau pathology, as measured by PET, across different brain regions showed that the mean difference in tau pathology was significant in the medial temporal (-0.068, p=0.002), meta temporal (-0.07, p=0.012), and temporal areas (-0.065, p=0.016).[42] See Supplement Table D3.4.

P-tau was examined by CSF at baseline, week 53, and week 77, and plasma at baseline, week 53, and week 79. There was a significant reduction in p-tau (p-tau 181), measured via plasma sample and CSF, in the lecanemab group (-0.6 and -15.9 in plasma and CSF, respectively) compared to increases the placebo group (0.2 and 12.9 in plasma and CSF, respectively) (p<0.001 in both analyses).[35]

Neurogranin was examined by CSF at baseline, week 53, and week 77. There was a significant decline in neurogranin the lecanemab group compared to an increase in the placebo group (-71.9 vs 18.9, p<0.001).[42] Neurofilament light chain (NfL) was examined by CSF at baseline, week 53, and week 77, and plasma at baseline, week 53, and week 79. There was no significant treatment effect on both of the NfL measures.[42] All biomarker outcomes are provided in the Supplement Table D3.4.

Additional Harms

ARIA was assessed by MRI at baseline and five additional time points across the study. In terms of radiographic severity, ARIA was measured on a 3-point scale from mild-severe. Symptomatic ARIA-E was assessed by radiographic severity and self-reported symptoms (both participant and assessor were blinded to treatment group). If a patient experienced asymptomatic, radiographically mild ARIA-E, they continued the drug with additional MRIs at 30, 60, and 90 days after ARIA was identified. If ARIA-E worsened or became symptomatic, the study drug would be temporarily discontinued. If symptomatic or radiographically moderate or severe ARIA-E occurred, the study drug would be stopped, and MRI was conducted every 30 days until it had resolved. Upon resolution, participants resumed the study drug. If occurred more than twice, the participant would

be discontinued from the study. If severe ARIA-E was associated with serious adverse event, the study drug would be stopped permanently. Safety was also monitored in an unblinded manner by an independent monitoring committee.

As noted in the main report, participants in the lecanemab group reported more infusion-related reactions compared to the placebo group (26.4% vs 7.4%).[35] These reactions mostly occurred on the first dose (75%) and were mostly mild-moderate in severity (96%), with 0.8% participants in the lecanemab group reporting a severe infusion-related reaction.[43] See Table D3.11. Of those who had an infusion-related reaction, approximately 40% received preventative medications (i.e., anti-inflammatory drugs, antihistamines, or glucocorticoids) and there was a 35% recurrence rate which was similar regardless of whether the participant took the preventive medication or not.

CLARITY AD Open-label Extension Phase

At the time of this report, the open-label extension (OLE) phase is still ongoing. In this phase, clinical and safety assessments were conducted every six months. The safety MRI schedule followed the same schedule as the core phase (e.g., taken at week 9, 13, and 6 months) for the first six months and then every six months after. The management of ARIA was the same across the core and extension phase.

Phase II: G000-201

G000-201 was a Phase IIb multi-center, placebo-controlled, dose-ranging, randomized control trial that aimed to identify the most effective dose of lecanemab. Six doses of lecanemab (2.5 mg/kg biweekly, 5 mg/kg monthly, 5 mg/kg biweekly, 10 mg/kg monthly, 10 mg/kg biweekly) were tested versus placebo for 18 months.[92] This trial utilized a Bayesian response-adaptive randomization whereby there was a fixed period of randomization for the first 196 participants (N=28 in each lecanemab arm, and N=56 in placebo) and then the response-adaptive randomization was implemented to minimize the overall sample size and study duration. See section on "Bayesian adaptive randomization" below for additional description of this randomization procedure. The primary outcome was change in ADCOMS at 12 months. This trial also included an extension phase of the 10 mg/kg biweekly lecanemab dose only. Participants had an off-treatment period and then re-initiated treatment for up to 60 months. The primary outcome for the extension phase was to examine adverse events and change from baseline in biomarkers at 60 months. Inclusion/exclusion criteria and baseline characteristics are described in Table D3.1 in this Supplement.

Participants were included in the Phase IIb study if they were aged between 50 and 90 years with MCI due to Alzheimer's Disease or mild Alzheimer's Disease dementia, had objective impairment in episodic memory and MMSE score 22-30, had a positive amyloid loid as determined by PET or CSF [Aβ(1-42)], had a BMI greater than 17 and less than 35 at screening, and had a study partner. Participants were not able to use therapies such as: immunoglobulin therapy (6 months), biologic

drugs (6 months), and anticoagulants (e.g., warfarin, dabigatran for 7 days or 5 half-lives). Other exclusion criteria included any neurological condition that may be contributing to cognitive impairment, any psychiatric diagnosis or symptoms, contraindications to MRI, evidence of other clinically significant brain lesions, or being on any Alzheimer's Disease medication for less than 12 weeks.

There was a total of 854 participants who took part in the G00-201 trial (lecanemab n=609 and placebo n=245). Participants had a median age of 71.7 years (range from 50-90) with 64% described as MCI due to Alzheimer's disease. A total of 54.7% of participants were currently on Alzheimer's disease medication and 71.8% were ApoE ε4 carriers. Participants reported a mean ADCOMS of 0.38 (SD=0.17), mean MMSE of 25.7 (SD=2.4), mean CDR-SB of 2.95 (SD=1.42), and mean ADAS-Cog14 of 22.5 (SD=7.5).[92]

Bayesian Adaptive Randomization

The response-adaptive randomization aimed to find the simplest (e.g., monthly vs. biweekly) and most effective (e.g., 10 mg, 5 mg, etc.) dose (≥ 90% of the maximum treatment effect) and allocate more participants to this dose at each interim analysis, which was conducted every 50 participants.[93] The trial also monitored for futility (<5% posterior probability that most likely effective dose is superior to placebo by 25% for the first three interim analyses and increased to <7.5% once they had reached 350 participants) and success (from 350 participants: >95% posterior probability that effective dose was better than placebo, or at the end of the trial: lecanemab effect exceeds placebo rate by ≥25%) during the interim analyses. The modeling had two components used to estimate the primary endpoint at week 52 for the adaptive randomization. First, the investigators used a dose-frequency model that examined mean change from baseline. This Bayesian model used weak prior distributions for mean response and allowed borrowing/smoothing across neighboring doses and frequencies to provide a superior estimate of each treatment arm's effect. Second, the investigators used a longitudinal model that examined correlations between early ADCOMS scores and the 52-week outcome. To do this, the investigators used priors selected from historical data and a Bayesian imputation within Markov chain Monte Carlo to impute the 52-week data and update the dose-frequency response model at each interim analysis.[93] As a result, the size of the individual dose groups differed depending on the interim analyses.

Notable protocol changes occurred during this Phase II trial, during the randomization period of participants 300-350. The regulatory authority requested that ApoE ε4 carriers (approximately 70% of the overall population) no longer be administered the 10 mg/kg biweekly dose of lecanemab going forward, due to increased risk of ARIA. As a result, 25 participants who were ApoE ε4 carriers were discontinued as they were in the trial for less than six months, compared to 46 ApoE ε4 carriers who were already on this dose for longer than six months and were able to continue. [92] The

regulatory change may have enriched the intervention arm with participants in the lecanemab group expected to perform better.

Results

In this supplement, we primarily focus on reporting the results from the lecanemab 10 mg/kg biweekly dose versus placebo, as this is the dose that was used in the Phase III CLARITY AD trial. Where that data is not available, we provide pooled data from the 10 mg/kg biweekly and monthly lecanemab arms versus placebo.

Cognitive Outcomes

The primary outcome in G000-201 trial was the change from baseline in ADCOMS score at 12 months.

Bayesian analysis was used to examine the primary outcome (ADCOMS) at 12 months. The 10 mg/kg biweekly dose was identified as the most effective dose. The 10 mg/kg biweekly group had a 64% probability of being more effective than placebo with 25% less decline on ADCOMS at 12 months. This result did not meet the pre-specified 80% probability threshold and thus the primary outcome was not met. The 10 mg/kg biweekly group had a 76% probability of being more effective than placebo with 25% less decline on ADCOMS at 18 months (secondary outcome), which also did not meet the pre-specified 80% threshold. However, the 10 mg/kg biweekly group had a 97.6% and 97.7% probability of being superior to placebo at any magnitude on the ADCOMS at 12 and 18 months, respectively (Table D3.7-8.). Subgroup analyses were conducted for those who were ApoE ε4 carriers and non-carriers. In ApoE ε4 carriers, the 10 mg/kg biweekly group had a 93.6% probability of being more effective than placebo with 25% less decline on ADCOMS at 18 months and a 99.2% probability of being superior to placebo at any magnitude on the ADCOMS at 18 months. In contrast, non-carriers had 29% probability of being more effective than placebo with 25% less decline on ADCOMS at 18 months and a 63% probability of being superior to placebo at any magnitude on the ADCOMS at 18 months (Table D3.13). Thus, the analyses suggest a potential differential treatment effect for carriers versus non-carriers, with ApoE ε4 carriers experiencing a greater treatment effect. However, this subgroup analysis should be treated as exploratory as the ApoE ε4 carrier group consisted of 45 participants (non-carrier n=107) due to the regulatory changes that prevented ApoE ε4 carriers being randomized to the highest dose.

Bayesian analysis was also used to examine other secondary outcomes (CDR-SB and ADAS-Cog14 at 18 months). At 18 months, the 10 mg/kg biweekly group had a 96.4% probability of being superior to placebo at any magnitude on the CDR-SB and a 98.8% probability of being superior to placebo at any magnitude on the ADAS-Cog14 (Table D3.14-15).

Alongside Bayesian analyses, frequentist mixed effect model with repeated measures (MMRM) were conducted for secondary outcomes comparing placebo to the lecanemab arms at 18 months. The MMRM included the following variables in the analysis: treatment group, visit, clinical subgroup (MCI due to AD, Mild AD dementia), the presence or absence of ongoing AD treatment at baseline, ApoE ε4 status, world region, and treatment group by visit interaction as factors, and baseline value of the cognitive outcome as covariate. The analysis did not correct for multiplicity. Additional sensitivity MMRM analyses were conducted, such as including the interaction between ApoE4-by-treatment-by-visit interaction which were important as randomization was broken and would have accounted for baseline risk and rate of change differences. In a manuscript that compared the Bayesian analysis to the MMRM analysis in the G000-201 trial, the authors reported consistency of the cognitive effects across the two statistical methodologies and that Bayesian analysis was useful in accommodating missing data from the protocol change imposed by the regulatory authority.[94]

Participants who received lecanemab 10 mg/kg biweekly had less cognitive decline in ADCOMS, as represented by a smaller increase in the score, at 12 months compared to placebo, mean difference versus placebo: -0.05; 95% CI: -0.8 to -0.01; p=0.027.[92] These results were consistent at 18 months with those in the lecanemab group showing 29.7% reduction in cognitive decline as compared to placebo (37.4% in the MMRM analysis that included ApoE4 status and visit interaction)[94], mean difference versus placebo: -0.06; 95% CI: -0.10 to -0.01; p=0.034 (Tables D2.1. and D3.4-5).

There was no significant treatment benefit of lecanemab 10 mg/kg biweekly on CDR-SB at 18 months, mean difference versus placebo of -0.396; 95% CI: -0.82 to 0.03; p=0.13 (Table D2.1).[92] There was a 26.5% reduction in cognitive decline on CDR-SB in lecanemab 10 mg/kg biweekly at 18 months compared to placebo (32.1% in the MMRM analysis that included ApoE4 status and visit interaction).[94] There was a significant treatment benefit of lecanemab 10 mg/kg biweekly on ADAS-Cog14 at 18 months for lecanemab as compared to placebo, with a mean difference of -2.31; 95% CI: -3.91 to -0.72; p=0.017.[92] There was a 47.2% reduction in cognitive decline on ADAS-Cog14 in lecanemab 10 mg/kg biweekly at 18 months compared to placebo (55.9% in the MMRM analysis that included ApoE4 status and visit interaction) (Table D3.4-5).[94]

Subgroup analyses reported data on the treatment benefit of lecanemab 10 mg/kg biweekly on cognitive outcomes (CDR-SB, ADCOMS, and ADAS-Cog14) for those with MCI due to AD or mild AD. The subgroup analyses provided conflicting results of efficacy (see Table D3.13.-15 for full details).[92] A subgroup analysis was also conducted on the ADCOMS outcome, specifically, and reported no difference in efficacy for Asian participants as compared to the full sample.[95] These analyses were conducted in small groups, likely underpowered, and thus should be considered exploratory.

Beta-amyloid

Decreases in beta-amyloid, as measured by Florbetapir PET SUVr, were significantly greater in the lecanemab 10 mg/kg biweekly group compared to placebo at 12 and 18 months (12 months: -0.26 vs placebo: -0.01, p<0.001; 18 months: -0.31 vs 0.004, p<0.001.[92,96] The investigators reported that 65% of those in the lecanemab 10 mg/kg biweekly group at 12 months and 81% at 18 months were amyloid negative by visual read.[96,97]

Decreases in plasma Aβ42/40 ratio were significantly greater in lecanemab 10 mg/kg biweekly group compared to placebo at 12 and 18 months (p<0.01).[96] There was also a significant increase in Aβ (1–42) in the pooled 10 mg/kg biweekly and monthly lecanemab group, compared to placebo (Table D3.4).[92] The investigators suggested that this increase may reflect changes in amyloid aggregation or normalization of amyloid levels. However, the analyses for these two outcomes were conducted in a subset of participants and thus it is not possible to infer conclusions about these data.

Other Biomarker Outcomes

In the pooled 10 mg/kg biweekly and monthly group, there was a significantly larger decrease in p-tau as compared to placebo at 18 months, mean difference: -12.3; p=0.013 (Table D3.4).[92] However, there were no significant differences in the change in t-tau, neurogranin nor in neurofilament light chain in the pooled group as compared to placebo.[92,98] These analyses were also conducted in a subset of participants and, as previously noted, it is not possible to infer conclusions from these data.

Brain volume was assessed using MRI scans at screening and months 6, 12, and 18. Volumetric MRI data was available for 72 participants in the lecanemab 10 mg/kg biweekly group and 162 participants in the placebo group. There was a greater decrease in whole brain volume in the lecanemab 10 mg/kg biweekly group compared to the placebo group at 18 months (mean difference: -8118.34 mm^3; 95% CI: -10538.26 to -5698.42, p=0.001) (Table D3.4). There was a greater increase ventricular volume in the lecanemab 10 mg/kg biweekly group compared to the placebo group at 18 months (mean difference: 2317.96 mm^3; 95% CI: 1678.88 to 2957.03, p=0.001). There was no significant difference between the groups in change in hippocampus volume at 18 months (mean difference: -19.44 mm^3; 95% CI: -46.77 to 7.88; p=0.24).[92]

Table D2.1. Key Trial Results

Measure		Lecanemab (G000-201)	
		Intervention (10 mg/kg Q2W)	Placebo
CDR-SB	Timepoint	12 months	
	Baseline (SD)	3.0 (1.4)	2.9 (1.5)
	N	84	161
	Mean change (SE)	1.10 (0.21)	1.5 (0.16)
	Difference in mean change (95% CI)	-0.396 (-0.82 to 0.03)	REF
ADCOMS	Timepoint	12 months	
	Baseline (SD)	0.37 (0.15)	0.37 (0.17)
	N	93	187
	Mean change (SE)	0.09 (0.02)	0.13 (0.01)
	Difference in mean change (95% CI)	-0.05 (-0.08 to -0.01)	REF
	Timepoint	18 months	
	N	79	160
	Mean change (SE)	0.14 (0.02)	0.19
	Difference in mean change (95% CI)	-0.06 (-0.10 to -0.01)	REF

Note. Ranges for cognitive scores at baseline were not reported. ADCOMS: AD composite score, CDR-SB: Clinical Dementia Rating scale Sum of Boxes, CI: confidence interval, mg: milligram, kg: kilogram, Q2W: every two weeks, SD: standard deviation, SE: standard error

Harms

Total adverse events, serious events, and deaths were similar across the lecanemab 10 mg/kg biweekly and placebo groups. The rate of total discontinuation was greater in the lecanemab 10 mg/kg biweekly group compared to placebo (14.9% vs 6.1%).[92] There was a higher prevalence of discontinuation due to adverse events in the lecanemab 10 mg/kg biweekly group compared to placebo (13.7% vs 6.1%), with most of the adverse events in the lecanemab group relating to ARIA-E (Supplement Table D2.2). Several participants discontinued due to "other" reasons which the investigators described as due to the regulatory change (ApoE ε4 carriers in the highest dose and were on treatment for less than six months were discontinued from treatment), subject moving out of the area, or the loss of a study partner. The lecanemab 10 mg/kg biweekly group were also more likely to experience infusion-related reaction compared to placebo (19.9% vs 3.3%). From this, there were 2.5% of participants in lecanemab 10 mg/kg biweekly who discontinued due to infusion-related reactions, compared to 0.80% in the placebo group.[99]

ARIA was assessed by MRI at baseline and seven additional time points across the study. In the core phase, if a patient experienced ARIA-E they would be discontinued from treatment. During the open-label extension phase, if ARIA-E was asymptomatic or radiographically mild-moderate then the participant could continue with monitoring. If symptomatic or radiographically severe, then treatment would be paused until ARIA-E resolved and then treatment could be resumed. If

occurring more than twice, the participant would have been discontinued from the treatment. During the open-label extension phase, the protocol was slightly different to the core phase in that if ARIA-E was mild-moderate or asymptomatic then participants could continue the intervention with monitoring. But, if ARIA-E was severe or symptomatic, then the intervention was temporarily discontinued for these participants until ARIA was resolved and then they restarted on the same dose.

A total of 9.9% participants in the lecanemab 10 mg/kg biweekly group experienced ARIA-E, compared to 0.8% in the placebo group. Due to the protocol change that prevented ApoE ε4 carriers being randomized to the highest dose, only 30% of participants in the 10 mg/kg biweekly were ApoE ε4 carriers and thus it is not possible to examine the true prevalence of ARIA-E in ApoE ε4 carriers in this dose. To provide some estimation as to the prevalence of ARIA-E in ApoE ε4 carriers, we reviewed ARIA in the second highest dose. In the 10 mg/kg monthly dose, 9.9% of participants experienced ARIA-E and 92% of those participants were ApoE ε4 carriers. All ARIA-E events in the lower lecanemab doses occurred in ApoE ε4 carriers. Additionally, there were 6.8% in the lecanemab 10 mg/kg biweekly group and 11.1% in the 10 mg/kg monthly dose who experienced ARIA-H, compared to 5.3% in the placebo group. There were 4.3% and 5.1% of participants in the lecanemab 10 mg/kg biweekly and 10 mg/kg monthly groups who experienced ARIA-E with ARIA-H, compared to 0.4% in placebo (Supplement Table D2.2).

As noted in the main report, symptomatic ARIA-E was of particular interest. Symptomatic ARIA-E was reported to generally consist of headache, visual disturbances, or confusion.[92] Symptomatic ARIA-E occurred in more participants in the lecanemab 10 mg/kg biweekly group (1.2%) and in 11% of all lecanemab doses, compared to no cases in the placebo group. There were no cases of symptomatic ARIA-H in the lecanemab or placebo groups. Per protocol requirements, all those who experienced symptomatic ARIA-E were discontinued from the treatment. The investigators provided no further information on the prevalence of symptomatic ARIA-E in ApoE ε4 carriers and thus we were not able to examine this.

Table D2.2. Adverse Events

Adverse event	Lecanemab (G000-201)					
	Lecanemab 2.5 mg/kg Q2W	Lecanemab 5 mg/kg Q4W	Lecanemab 5 mg/kg Q2W	Lecanemab 10 mg/mg Q4W	Lecanemab 10 mg/kg Q2W	Placebo
Any Adverse Event, n/N (%)	46/52 (88.5%)	48/51 (94.1%)	81/92 (88.0%)	238/253 (94.1%)	139/161* (86.3%)	216/245 (88.2%)
Serious Adverse Event, n/N (%)	10/52 (19.2%)	4/51 (7.8%)	16/92 (17.4%)	31/253 (12.3%)	25/161 (15.5%)	43/245 (17.6%)
Discontinuation Due to Adverse Event, n/N (%)	7/52 (13.5%)	4/51 (7.8%)	10/92 (10.9%)	47/253 (18.6%)	24/161 (14.9%)	15/245 (6.1%)
Any ARIA-E, n/N (%)	1/52 (1.9%)	1/51 (2.0%)	3/92 (3.3%)	25/253 (9.9%)	16/161 (9.9%)	2/245 (0.8%)
Symptomatic ARIA-E, n/N (%)	1/52 (1.9%)	0/51 (0)	1/92 (1.09%)	1/253 (0.4%)	2/253 (0.8%)	0/245 (0)
Any ARIA-H, n/N (%)	2/52 (3.8%)	7/51 (13.7%)	17/92 (18.5%)	28/253 (11.1%)	11/161 (6.8%)	13/245 (5.3%)

ARIA: Amyloid-related imaging abnormalities, mg/kg: milligram per kilogram, N: number of participants, Q2W: biweekly (once every two weeks), Q4W: once every month

*Incorrectly reported in Swanson et al. (2021) as 39/161.

G000-201 Open-label Extension Phase

The OLE phase included 130 participants from the core study (n=42 in prior placebo group, n=37 in prior 10mg/kg biweekly group, and the remaining 101 participants were in the other lecanemab doses).[100] Baseline characteristics for the extension phase are reported in Supplement Table D3.3. Of note, at the OLE baseline, the majority of those who had received lecanemab 10 mg/kg biweekly during the core phase and continued onto the OLE phase were ApoE4 non-carriers (91.9%). While it is expected that there would be fewer ApoE4 carriers in this group due to the regulatory changes that prevented ApoE4 carriers being randomized to this dose early in the trial, only 3 out of 46 ApoE4 carriers in this dose continued onto the OLE extension. It is unclear the reason behind participants not continuing onto the extension phase, but may relate to tolerability, adverse events, such as ARIA, or lack of efficacy. Connected to this final reason, participants who received lecanemab 10 mg/kg biweekly during the core phase and continued onto the extension phase had lower levels of amyloid (as measured by centiloids) at extension phase baseline compared to placebo and those who received any of the other lecanemab doses. However, the standard deviation of the mean centiloids was very large suggesting that there was considerable heterogeneity in the clearance of amyloid in this group.

All participants had a gap period off-treatment, with a mean duration off the study drug of 23.7 months (range: 9.2 to 52.5).[96] During the gap period, cognitive ability, as measured by ADCOMS, worsened in all groups with a similar rate of progression across both those who did or did not receive lecanemab in the core phase, and amyloid, Aβ42/40, and p-tau increased in those treated with lecanemab during the core phase (Table D3.6). During the OLE period, participants received lecanemab 10 mg/kg biweekly, including ApoE ε4 carriers, for up to 60 months. Clinical assessments were administered every six months. Once redosing begin during the OLE phase, amyloid, Aβ42/40, and p-tau decreased in the two groups (those treated with lecanemab or placebo during the core phase).[96,100] At month 12, by visual read, 83% (n=10) of those in the core placebo treated group had converted to amyloid negative status.[100] In terms of clinical outcomes, by 18 months, participants in both groups showed a similar rate of clinical decline.[100] See Table D3.4. It is to be noted that these analyses were based upon very small numbers and thus caution should be taken in interpreting these values.

In terms of harms, safety assessments were monitored slightly differently to the core phase. Hematology, blood chemistry, and urinalysis were assessed at baseline, weeks 3, 7, 13, 19, 27, and every 6 months thereafter. ARIA was also monitored and managed slightly differently to the core phase. In this phase, safety MRIs were taken at baseline, week 9, 13, 27, and every 6 months thereafter. In this phase, if ARIA-E was mild-moderate or asymptomatic then participants could continue with treatment. If severe or symptomatic, dosing was paused until ARIA resolved and then participants could restart treatment. ARIA rates were similar to the core phase with 7.8% of ARIA-E in lecanemab core phase treated participants and 8.9% in placebo core phase treated participants, all of whom were ApoE ε4 carriers, with around 2% having symptomatic ARIA.[96,101] Similar to the core phase, most ARIA-E occurred within first 3 months and resolved within 12 weeks. At the time of this report, the investigators reported that 6/14 mild-moderate cases continued treatment through ARIA. A total of 20.6% had infusion-related reactions during the OLE phase that were mostly mild-moderate.[99]

Phase I: Subcutaneous Dose

An open-label parallel-group trial including 59 healthy participants was conducted to examine the bioavailability, pharmacokinetics, safety, and immunogenicity of a single 700 mg subcutaneous (SC) dose of lecanemab. There were 30 participants who received IV infusion and 29 received SC injection. In terms of safety, adverse events were comparable across the two dosage forms and 20.7% in the SC dose group reported injection-site reactions, compared to 33.3% reporting infusion-related reactions in the IV dose group (Table D3.12).[102] Investigators concluded that SC dosing appears to be a potentially feasible option to progress into Phase II trials.

D3. Evidence Tables

Table D3.1. Study Design

Trial	Study Design	Treatment Arms	Background Therapy	Included Patients	Excluded Patients	Key Outcomes [Timepoints]
Lecanemab						
AHEAD 3-45 ClinicalTrials.gov	Phase III, QB, RCT	LCB 5 mg + 10 mg Q2W LCB 5 mg + 10 mg Q4W PBO	Background Therapy Unclear Prohibited Therapies Anti-amyloids, immunoglobin therapy, lecanemab, new chemical entities, investigational medications	- Aged 55 to 80 years - 55 to 64 must have additional risk factors such as first degree relative diagnosed with dementia, possesses at least 1 APOE4 - CDR score of 0 - MMSE score >= 27 - WMS-R LM II >6	- History of ischemic attacks - Current history of psychiatric diagnosis or symptoms that could interfere with study procedures - HIV positive	Primary: Change in PACC5, change in PET [216 weeks] Secondary: Change in PET, CFI [96/216 weeks]
CLARITY AD ClinicalTrials.gov, Swanson et al CTAD 2021[96]	Phase III, PC + OLE phase	LCB 10 mg Q2W LCB 10 mg Q2W (extension phase) PBO	Background Therapies Stable dose of concomitant AD treatment for <= 12 weeks prior to baseline, treatment-naïve subjects are eligible Prohibited Therapies Immunoglobins, systemic monoclonal antibodies,	Core Study Objective impairment in episodic memory as indicated by at least 1 standard deviation below age-adjusted mean in the Wechsler Memory Scale IV-Logical Memory (subscale) II (WMS-IV LMII) Positive biomarker for brain amyloid pathology Male or female participants aged greater than or equal to (>=) 50 and less than or equal to (<=) 90 years, at the time of informed consent	Any neurological condition that may be contributing to cognitive impairment above and beyond that caused by the participant's Alzheimer's disease History of transient ischemic attacks (TIA), stroke, or seizures within 12 months of Screening Any psychiatric diagnosis or symptoms (example, hallucinations, major depression, or delusions) that could interfere with study procedures in the participant	Primary (core study): Change from baseline in CDR-SB [18 months] Primary (extension): AEs, change in CDR-SB [45 months] Secondary (core): Change in amyloid PET, ADAS-Cog14, ADCOMS, and ADCS-MCI-ADL at 18 months

				Mini mental state examination (MMSE) score ≥22 at Screening and Baseline and ≤30 at Screening and Baseline Body mass index (BMI) greater than (>)17 and less than (<) 35 at Screening <u>Extension phase</u> - Completed core study <u>Other:</u> - Positive biomarker MMSE >22 <30 BMI >17, <35	Geriatric Depression Scale (GDS) score ≥8 at Screening Contraindications to MRI scanning, including cardiac pacemaker/defibrillator, ferromagnetic metal implants (example in skull and cardiac devices other than those approved as safe for use in MRI scanners) Evidence of other clinically significant lesions on brain MRI at Screening that could indicate a dementia diagnosis other than Alzheimer's disease	
Phase II G000-201 Swanson, et al 2021[92]	Phase IIb, MC, DB, PC	LCB 2.5 mg Q2W LCB 5.0 mg Q4W LCB 5.0 mg Q2W LCB 10 mg Q4W LCB 10 mg Q2W PBO	<u>Background Therapies</u> Stable dose of approved AD medications or treatment naïve <u>Prohibited Therapies</u> Immunoglobulin therapy (6 months), Biologic drugs (6 months), and Anticoagulants (eg, warfarin, dabigatran for 7 days or 5 half-lives, whichever is longer)	- AD due to MCI or mild AD dementia - Confirmed amyloid positive via Aβ1-42: PET or CSF - Impairment in episodic memory (WMS-IV LMII - MMSE ≥22 - Naïve or stable dose of approved AD medications	- Any medical or neurological condition (other than Alzheimer's Disease) that might be a contributing cause of the subject's cognitive impairment - Have had a stroke or Transient Ischemic Attack, stroke, or seizures in the past 1 year - Any psychiatric diagnosis or symptoms that could interfere with study procedures - GDS score ≥8 - Contraindications to MRI scanning - Evidence of other clinically significant lesions that could indicate a dementia	Primary: Change from baseline on ADCOMS [12 months] Secondary: Change from baseline in ADCOMS [18 months], CDR-SB, ADAS-cog14, brain amyloid PET, hippocampal, ventricular, and whole-brain volume via MRI [12 and 18 months], and exploratory biomarkers [12 and 18 months]

					diagnosis other than AD - Prolonged QT/QTc interval via ECG - Other medical conditions that could prevent patient performing tests accurately	

Phase II G000-201 OLE Clinicaltrials.gov	Phase II, DB, PC, OLE	LCB 10 mg Q2W Off-treatment period (9-59 months, average 24 months) before re-initiating treatment for 60 months	Background Therapies Unclear Prohibited Therapies Immunoglobulin therapy (6 months), Biologic drugs (6 months), if on thrombolytic drugs study drug will be temporarily suspended until stabilization or resolution of the medical condition, if on anticoagulants at OLE baseline then anticoagulation status optimized and stable for at least 4 weeks before OLE screening.	- AD due to MCI or mild ALZ dementia - Confirmed amyloid positive via Aβ1-42: PET or CSF - Impairment in episodic memory (WMS-IV LMII - MMSE ≥22 - Naïve or stable dose of approved ALZ medications	- Any medical or neurological condition (other than Alzheimer's Disease) that might be a contributing cause of the subject's cognitive impairment - Have had a stroke or Transient Ischemic Attack, stroke, or seizures in the past 1 year - Any psychiatric diagnosis or symptoms that could interfere with study procedures - GDS score ≥8 - Contraindications to MRI scanning - Evidence of other clinically significant lesions that could indicate a dementia diagnosis other than AD - Prolonged QT/QTc interval via ECG - Other medical conditions that could prevent patient performing tests accurately	Primary: Safety data and MRI assessments of ARIA [up to 78 months] Secondary: Change from baseline on brain amyloid levels [3, 6, 12, and 24 months], change in brain amyloid from end of core study to baseline of extension phase, percentage of amyloid positive participants over time]up to 60 months]. Change in ADCOMS, CDR-SB, ADAS-cog14 [up to 60 months].

Phase 1 - Single, Fixed Subcutaneous Dose (Doung et al. 2022 - AAIC Conference Abstract) [102]	Phase I, open-label, parallel-group study	Single fixed 700 mg SC dose in the abdomen; IV dose after single dose of 10 mg/kg IV infused over approximately 1 hour	NR	Healthy participants.	NR	Outcomes: Absolute bioavailability (BA), pharmacokinetics (PK), safety and immunogenicity

AChEIs: acetylcholinesterase inhibitor, AD: Alzheimer's disease, ADCOMS: AD Composite Score, ADAS-Cog14: Alzheimer's Disease Assessment Scale – Cognitive Subscale 14-item, ARIA: amyloid-related imaging abnormalities, ADCS-MCI-ADL: Alzheimer's Disease Cooperative Study – Activities of Daily Living Inventory (MCI version), CFI: Cognitive Function Index, CDR: Clinical Dementia Rating, CDR-SB: Clinical Dementia Rating – Sum of Boxes, DB: double-blind, ECG: electrocardiogram, IV: intravenous, LCB: lecanemab, MMSE: mini mental state examination, MG: milligram, MC: multicenter, MCI: mild cognitive impairment, mg/kg: milligram per kilogram, MRI: magnetic resonance imaging, NR: not reported, OLE: open-label extension, PACC5: Preclinical Alzheimer Cognitive Composite 5, PC: placebo-controlled, PET: Positron Emission Tomography, Q2W: every two weeks, Q4W: every four weeks, SC: subcutaneous, WMS-IV: Wechsler Memory Scale – Fourth Edition.

Table D3.2. Baseline Characteristics

Trial		G000-201			CLARITY AD	
Source		**Swanson et al. 2021[92]**			**van Dyck et al. 2022[35]; CTAD Conference 2022 (Iziarry et al. 2022)[103]**	
Study Arms		Lecanemab 10 mg/kg Q4W	Lecanemab 10 mg/kg Q2W	Placebo	Lecanemab 10 mg/kg Q4W	Placebo
N		246	152	238	859‡	875‡
Age, Mean (SD)		71 (53-90)†	73 (51-88)†	72 (50-89)	71.4 (7.9)	71.0 (7.8)
Female, n (%)		110 (45)	64 (42)	137 (58)	443 (51.6)	464 (53.0)
Race, n (%)	Asian	NR	NR	NR	147 (17.1)	148 (16.9)
	Black	NR	NR	NR	20 (2.3)	24 (2.7)
	White	NR	NR	NR	655 (76.3)	677 (77.4)
	Other	NR	NR	NR	37 (4.3)§	26 (3.0)§
Ethnicity, n(%)	Hispanic/Latino	NR	NR	NR	107 (12.5)	108 (12.3)
	Non-Hispanic/Latino	NR	NR	NR	NR	NR
Concomitant AD Medication, n(%)	Cholinesterase Inhibitors and/OR Memantine	131 (53)	79 (52)	128 (54)	447 (52.0)	468 (53.5)
Other Medication, n (%)	Anticoagulants	NR	NR	NR	80/1795 (4.5)	
ApoE4 Status, n(%)	Carrier	218 (89)	46 (30)	169 (71)	592 (68.9)	600 (68.6)
APOE Genotype, n/N (%)	e3/e4 (heterozygote)	NR	NR	NR	456 (53.1)	468 (53.5)
	e4/e4 (homozygote)	NR	NR	NR	136 (15.8)	132 (15.1)
Clinical Stage, n(%)	MCI due to AD	166 (68)	90 (59)	154 (65)	528 (61.5)	544 (62.2)
	Mild AD	NR	NR	NR	331 (38.5)	331 (37.8)
Comorbidities, n (%)	Hypertension	NR	NR	NR	993/1795 (55.3)	
	Hyperlipidemia	NR	NR	NR	1085/1795 (60.4)	
	Ischemic heart disease	NR	NR	NR	291/1795 (16.2)	
	Diabetes	NR	NR	NR	271/1795 (15.1)	
	Obesity	NR	NR	NR	298/1795 (16.6)	
	2+ comorbidities	NR	NR	NR	917/1795 (51.1)	
	3+ comorbidities	NR	NR	NR	441/1795 (24.6)	

	4+ comorbidities	NR	NR	NR	139/1795 (7.7)	
	5+ comorbidities	NR	NR	NR	25/1795 (1.4)	
CDR Global Score, n(%)	0.5	210 (85)	133 (88)	200 (84)	694 (80.8)	706 (80.7)
	1	NR	NR	NR	165 (19.2)	169 (19.3)
MMSE Score, Mean (SD)		25.7 (2.4)	25.6 (2.4)	26.0 (2.3)	25.5 (2.2), 22 to 30	25.6 (2.2) 22 to 30
CDR-SB Score, Mean (SD), Range		2.9 (1.3)	3.0 (1.4)	2.9 (1.5)	3.17 (1.34), 0.5 to 8.0	3.22 (1.34), 0.5 to 8.5
ADAS-Cog14 Score, Mean (SD)		21.9 (7.3)	22.1 (7.7)	22.6 (7.7)	24.45 (7.08)	24.37 (7.56)
ADCS-MCI-ADL Score, Mean (SD)		NR	NR	NR	41.2 (6.6)	40.9 (6.9)
ADCOMS Score, Mean (SD)		0.37 (0.15)	0.37 (0.15)	0.37 (0.17)	0.398 (0.147)	0.400 (0.147)
CSF	Aβ42/40, pg/ml, Mean (SD)	NR	NR	NR	0.047	0.044
	Aβ1-42, pg/ml, Mean (SD)				547.00	514.40
	Aβ1-40, pg/ml, Mean (SD)				11987.00	12334.00
	t-tau, pg/ml, Mean (SD)	NR	NR	NR	585.00	615.00
	p-tau, pg/ml, Mean (SD)	NR	NR	NR	84.92	92.08
	Neurofilament Light Chain, pg/ml, Mean (SD)	NR	NR	NR	1201	1109

Plasma	Aβ42/40, Mean (SD)	NR	NR	NR	0.088	0.088
	Neurofilament Light Chain, mean (SD)	NR	NR	NR	21.9	22.2
	p-tau, Mean (SD)	NR	NR	NR	3.70	3.74
PET	Centiloids, mean (SD), range	90.3 (41.5)*	78.0 (38.0)*	84.8 (37.4)*	77.92 (44.84), -16.6 to 213.2#	75.03 (41.82), -17.0 to 179.6#
	SUVr, Mean (SD)	1.42 (0.18)	1.37 (0.16)	1.40 (0.16)	NR	NR

AD: Alzheimer's disease, ADCOMS: AD Composite Score, ADAS-Cog14: Alzheimer's Disease Assessment Scale – Cognitive Subscale 14-item, ApoE: Apolipoprotein E, MMSE: mini mental state examination, ADCS-MCI-ADL: Alzheimer's Disease Cooperative Study – Activities of Daily Living Inventory (MCI version), CSF: cerebrospinal fluid, CTAD: Clinical Trials on Alzheimer's Disease, CDR: Clinical Dementia Rating, CDR-SB: Clinical Dementia Rating – Sum of Boxes, kg: kilogram, mg/kg: milligram per kilogram, MCI: mild cognitive impairment, NR: not reported, N: number, PBO: placebo, PET: positron emission tomography scan, p-tau: phosphorylated tau, pg/ml: picograms per milliliter, SD: standard deviation, SUVr: standardized uptake value ratio, %: percent

*Amyloid PET substudy: n=99 placebo, n=89 10 mg/kg monthly, n=44 10 mg/kg biweekly.[100]

†Median (range)

‡mITT

§Other/missing

#Amyloid PET substudy population n= 354 lecanemab, n = 344 (placebo).

Table D3.3. Baseline Characteristics of G000-201 OLE

Trial		**G000-201 OLE**		
Source		**McDade et al. 2022[100]**		
Study Arms		Prior core placebo	Prior lecanemab 10 mg/kg Q2W	Lecanemab 10 mg/kg Q2W
N		42	37	180*
Age, Mean (SD)		71.8 (8.2)	76.9 (7.0)	74.0 (7.7)
Female, n (%)		21 (50.0)	18 (48.6)	87 (48.3)
ApoE4 Status, n(%)	Carrier	30 (71.4)	3 (8.1)	125 (69.4)
	e3/e4 (Heterozygote)	4 (9.5)	0	97 (53.9)
	e4/e4 (Homozygote)	26 (61.9)	3 (8.1)	28 (15.6)
	Noncarrier	12 (28.6)	34 (91.9)	55 (30.6)
Clinical Stage, n(%)	MCI due to AD	27 (64.3)	22 (59.5)	110 (61.1)
	Mild AD	15 (35.7)	15 (40.5)	70 (38.9)

CDR Global Score, n(%)	0.5	19 (45.2)	19 (51.4)	80 (44.4)
	1	18 (42.9)	11 (29.7)	68 (37.8)
MMSE Score, Mean (SD)		21.5 (6.3)	21.2 (6.0)	20.7 (6.6)
CDR-SB Score, mean (SD), range		4.7 (3.2)	5.0 (3.7)	5.3 (3.5)
ADAS-Cog14 Score, mean (SD)		33.4 (13.5)	32.5 (13.8)	35.1 (14.0)
ADCOMS Score, mean (SD)		0.6 (0.3)	0.6 (0.4)	0.7 (0.4)
Florbetapir PET	Centiloids, mean (SD), range	77.2 (42.0)	8.6 (30.9)	44.5 (43.9)
	SUVr, Mean (SD)	1.4 (0.2)†	1.1 (0.1)†	1.2 (0.2)†

AD: Alzheimer's disease, ADCOMS: AD Composite Score, ADAS-Cog14: Alzheimer's Disease Assessment Scale – Cognitive Subscale 14-item, ApoE: Apolipoprotein E, MMSE: mini mental state examination, ADCS-MCI-ADL: Alzheimer's Disease Cooperative Study – Activities of Daily Living Inventory (MCI version), CSF: cerebrospinal fluid, CTAD: Clinical Trials on Alzheimer's Disease, CDR: Clinical Dementia Rating, CDR-SB: Clinical Dementia Rating – Sum of Boxes, kg: kilogram, mg/kg: milligram per kilogram, MCI: mild cognitive impairment, NR: not reported, N: number, PBO: placebo, PET: positron emission tomography scan, p-tau: phosphorylated tau, pg/ml: picograms per milliliter, SD: standard deviation, SUVr: standardized uptake value ratio, %: percent

*180 entered OLE with 45 previously receiving placebo, 38 lecanemab 10mg/kg biweekly, and 97 receiving different lecanemab doses.

†Amyloid PET substudy: n=27 prior placebo, n=21 prior core 10BW

Table D3.4. Lecanemab Outcomes

Trial		**G000-201**				**CLARITY AD**	
Source		**Swanson et al. 2021[92]; Dhadda et al. 2022[94]; Berry et al. CTAD conference 2021 [104]; Swanson et al. CTAD conference 2021 [96]; Swanson 2018 ALZ & Dementia[97]; Molinuevo et al. 2019[98]**				**van Dyck et al. 2022; CTAD conference 2022[35,47]**	
Study Arms		Lecanemab 10 mg/kg monthly	Lecanemab 10 mg/kg biweekly	Placebo	Lecanemab pooled 10 mg/kg	Lecanemab 10 mg/kg Q4w	Placebo
Baseline N		246	152	238	398	1795	
Timepoint		**18 months**					
Cognitive Outcomes							
CDR-SB Score	N	149	84	161	233	714	757
	LS Mean Change (SE)	1.248 (0.17)	1.102 (0.21)	1.499 (0.16)	1.171 (0.136)	1.21	1.66
	Diff (95% CI)	-0.250 (-0.613 to 0.112)*	-0.396 (-0.821 to 0.028)	REF	-0.302 (-0.620 to 0.017)	-0.45 (-0.67 to -0.23)	REF

	P-value	0.255	0.125	REF	0.119	p<0.001	REF
	Reduction in cognitive decline vs. PBO	16.7%; p=0.255	26.5%; p=0.125	NR	NR	27%	REF
ADAS-Cog14 Score	N	146	79	158	225	703	738
	LS Mean Change (SE)	4.624 (0.65)	2.588 (0.81)	4.902 (0.62)	3.735 (0.549)	4.14	5.58
	Diff (95% CI)	-0.278 (-1.635 to 1.079)*	-2.313 (-3.910 to -0.717)	REF	-1.064 (-2.290 to 0.163)	-1.44 (-2.27 to -0.61)	REF
	P-value	0.736	0.017	REF	0.154	p<0.001	REF
	Reduction in cognitive decline vs. PBO	5.7%; p=0.736	47.2%; p=0.017	NR	NR	26%	REF
ADCOMS	Timepoint	12 months				NR	NR
	N	165	93	187	258	NR	NR
	LS Mean Change (SE)	0.102 (0.01)	0.085 (0.02)	0.131 (0.01)	0.093 (0.012)	NR	NR
	Diff (90% CI)	-0.029 (-0.057, 0.000)	-0.046 (-0.079 to -0.012)	REF	-0.035 (-0.060 to -0.010)	NR	NR
	P-value	0.101	0.027	REF	0.019	NR	NR
	Timepoint	18 months				18 months	
	N	146	79	160	225	708	749
	LS Mean Change (SE)	0.166 (0.02)	0.136 (0.02)	0.193	0.152 (.014)	0.164	0.214
	Diff (90% CI)	-0.028 (-0.065 to 0.010)	-0.057 (-0.102 to -0.013)	REF	-0.039 (-0.071 to -0.006)	-0.05 (-0.074 to -0.027)	REF
	P-value	0.228	0.034	REF	0.053	p<0.001	REF
	Reduction in cognitive decline vs. PBO	14.3%, p=0.228	29.7%, p=0.034	REF	NR	24%	REF
ADCS-MCI-ADL Score	N	NR	NR	NR	NR	676	707
	LS Mean Change (SE)	NR	NR	NR	NR	-3.5	-5.5
	Diff (95% CI)	NR	NR	NR	NR	2.0 (1.2 to 2.8)	REF
	P-value	NR	NR	NR	NR	p<0.001	REF
	Reduction in cognitive decline vs. PBO	NR	NR	NR	NR	37%	REF
Amyloid Outcomes							

PET centiloids	Timepoint	NR	NR	NR	NR	18 months	
	N	NR	NR	NR	NR	210†	205†
	Mean (SD)	NR	NR	NR	NR	22.99	
	LS Mean Change (SE)	NR	NR	NR	NR	-55.48	3.64
	Difference in Mean Change (SE)	NR	NR	NR	NR	-59.12	REF
	95% CI	NR	NR	NR	NR	-62.64 to -55.60	REF
	P-value	NR	NR	NR	NR	p<0.001	REF
	Percent of reduction	NR	NR	NR	NR	NR	NR
	Effect size	NR	NR	NR	NR	NR	NR
	Amyloid Negative, n(%)	NR	NR	NR	NR	68 (32.4%)‡	16 (7.8%)
Florbetapir PET SUVr	Timepoint	12 months				NR	NR
	N	NR	43	96	NR	NR	NR
	Adjusted Mean Change	NR	-0.26	-0.01	NR	NR	NR
	95% CI	NR	NR	NR	NR	NR	NR
	Percentage reduction	NR	NR (65)	NR	NR	NR	NR
	P-Value	NR	p<0.0001	REF	NR	NR	NR
	Timepoint	18 months				NR	NR
	N	82	37	88	119	NR	NR
	Adjusted Mean Change	-0.225	-0.3	0.004	-0.253	NR	NR
	95% CI	NR	NR	REF	NR	NR	NR
	Amyloid negative, n(%)	NR	NR (81)	NR	NR	NR	NR
	P-Value	NR	p<0.0001	REF	p<.001	NR	NR
MRI Outcomes							
Volumetric MRI: Whole Brain	N	144	72	162	NR	644	667
	LS Mean Change (SE)	-25030.19 (1017.49)	-29894.19 (1300.82)	-21775.86 (921.13)	NR	-21392.2	-17227.6
	Diff (95% CI)	-3254.34 (-5101.23 to -1407.44)*	-8118.34 (-10538.26 to -5698.42)	REF	NR	NR	NR

	P-value (Dunnett p-value)	0.004 (0.066)	0.001 (0.000)	REF	NR	p<0.0001	REF
Volumetric MRI: Ventricular Volume	N	144	72	161	NR	644	667
	LS Mean Change (SE)	6504.05 (267.76)	7662.46 (343.22)	5344.503	NR	7434.8	5655.7
	Diff (95% CI)	1159.55 (671.83 to 1647.27)*	2317.96 (1678.88 to 2957.03)	REF	NR	NR	NR
	P-value (Dunnett p-value)	0.001 (0.002)	0.001 (0.000)	REF	NR	p<0.0001	REF
Volumetric MRI: Hippocampus Volume	N	144	72	162	216	643	667
	LS Mean Change (SE)	-264.87 (11.45)	-276.74 (14.68)	-2.57.297	-266.644 (10.321)	-186.1	-205.2
	Diff (95% CI)	-7.57 (-28.42 to 13.28)*	-19.44 (-46.77 to 7.88)	REF	-11.324 (-30.434 to 7.787)	NR	NR
	P-value (Dunnett p-value)	0.550 (1.000)	0.24 (0.99)	REF	0.330 (0.909)	p=0.0039	REF
CSF & Plasma Outcomes							
CSF Aβ1-42, pg/ml	N	NR	NR	NR	NR	101	97
	Adjusted Mean Change	NR	NR	NR	205.6	281.8	-6.5
	Diff (95% CI)	NR	NR	NR	NR	NR	NR
	P-value	NR	NR	NR	<.001	NR	NR
CSF Aβ1-40, pg/ml	N	NR	NR	NR	NR	71	71
	Adjusted Mean Change	NR	NR	NR	NR	-417.9	-89.9
	Diff (95% CI)	NR	NR	NR	NR	NR	NR
	P-value	NR	NR	NR	NR	NR	NR
Plasma Aβ42/40 ratio	Timepoint	12 months			NR	NR	NR
	N	NR	39	82	NR	648	668
	Adjusted Mean Change	NR	0.005	0	NR	0.008	0.001
	Percent reduction	NR	NR	NR	NR	NR	NR
	Diff (95% CI)	NR	NR	NR	NR	NR	NR
	P-value	NR	p<0.01	REF	NR	NR	NR
	Timepoint	18 months			NR	NR	NR
	N	NR	33	39	NR	NR	NR
	Adjusted Mean Change	NR	0.008	0.002	NR	NR	NR

	Diff (95% CI)	NR	NR	NR	NR	NR	NR
	P-value	NR	p<0.01	REF	NR	NR	NR
CSF T-tau pg/ml	N	NR	NR	NR	NR	101	98
	Adjusted Mean Change	NR	NR	NR	18.8	-29.1	95.3
	Diff (95% CI)	NR	NR	NR	NR	NR	NR
	P-value	NR	NR	NR	0.67	p<0.0001	REF
Plasma P-tau, pg/ml	N	NR	NR	NR	NR	590	609
	LS Mean Change	NR	NR	NR	NR	-0.6	0.2
	Percent reduction	NR	NR	NR	NR	NR	NR
	Diff (95% CI)	NR	NR	NR	NR	NR	NR
	P-value	NR	NR	NR	NR	p<0.001	REF
CSF P-tau181	N	NR	NR	NR	23	101	98
	LS Mean Change	NR	NR	NR	-13.3	-15.9	12.9
	Percent reduction	NR	NR	NR	13%	NR	NR
	Diff (95% CI)	NR	NR	NR	-12.3 (4.7)	NR	NR
	P-value	NR	NR	NR	0.013	p<0.001	REF
CSF Neurogranin, pg/ml	N	NR	NR	16	23	104	97
	Adjusted Mean Change	NR	NR	7.089	-36.962	-71.6	18.9
	Percent reduction	NR	NR	NR	11%	NR	NR
	Diff (95% CI)	NR	NR	NR	-43.8 (29.5)	NR	NR
	P-value	NR	NR	NR	0.145	p<0.0001	REF
Plasma Neurofilament Light Chain, pg/ml	N	NR	NR	NR	NR	529	574
	Adjusted Mean Change	NR	NR	NR	NR	1.8	2.9
	Percent reduction	NR	NR	NR	NR	NR	NR
	Diff (95% CI)	NR	NR	NR	NR	NR	NR
	P-value	NR	NR	NR	NR	p=0.06	REF
CSF Neurofilament Light Chain, pg/ml	N	NR	NR	16	23	104	97
	Adjusted Mean Change	NR	NR	68.497	10.405	52.00	78.00
	Percent reduction	NR	NR	NR	48%	NR	NR
	Diff (95% CI)	NR	NR	NR	-58.7 (57.5)	NR	NR

	P-value	NR	NR	NR	0.313	NS	REF
Health-Related Quality of Life Measures							
EQ-5D-5L (participant)	N	NR	NR	NR	NR	715	754
	Adjusted Mean Change	NR	NR	NR	NR	-2.1	-4.2
	P value	NR	NR	NR	NR	p<0.01	REF
	Percent decline	NR	NR	NR	NR	-49%	REF
QOL-AD (participant)	N	NR	NR	NR	NR	715	753
	Adjusted Mean Change	NR	NR	NR	NR	-0.5	-1.2
	P value	NR	NR	NR	NR	p<0.01	REF
	Percent decline	NR	NR	NR	NR	-56%	REF
QOL-AD (participant by proxy)	N	NR	NR	NR	NR	713	754
	Adjusted Mean Change	NR	NR	NR	NR	-1.8	-2.3
	P value	NR	NR	NR	NR	p<0.05	REF
	Percent decline	NR	NR	NR	NR	-23%	REF
Zarit Burden Interview (Study partner burden)	N	NR	NR	NR	NR	712	755
	Adjusted Mean Change	NR	NR	NR	NR	3.6	5.8
	P value	NR	NR	NR	NR	p<0.0001	REF
	Percent decline	NR	NR	NR	NR	-38%	REF
Follow-Up Rates							
Discontinuation of treatment		92/253 (36.4)	71/161 (44.1)	57/247 (23.1)	NR	NR	NR
Discontinuation of trial		NR	NR	NR	NR	169/898 (18.8)	140/897 (15.6)

AD: Alzheimer's disease, ADCOMS: AD Composite Score, ADAS-Cog14: Alzheimer's Disease Assessment Scale – Cognitive Subscale 14-item, ADCS-MCI-ADL: Alzheimer's Disease Cooperative Study – Activities of Daily Living Inventory (MCI version), CDR-SB: Clinical Dementia Rating – Sum of Boxes, CI: confidence interval, LS; least squares, LCB: lecanemab, mg/kg: milligrams per kilogram, MRI: magnetic resonance imaging N: number, NR: not reported, PBO: placebo, REF: reference, SD: standard error, SE: standard error

*90% CI

†Amyloid PET substudy population n= 354 (lecanemab) n = 344 (placebo).

‡<30 cl

Table D3.5 Outcomes (Lower doses of G000-201 Study)

Source		Swanson et al. 2021[92]		
Study Arms		LCB 2.5 mg/kg biweekly	LCB 5 mg/kg monthly	LCB 5 mg/kg biweekly
Baseline N		52	48	89
Timepoint		**18 months**		
Cognitive Outcomes				
CDR-SB Score	N	34	36	67
	LS Mean Change (SE)	1.227 (0.34)	1.713 (0.33)	1.463 (0.25)
	Diff (95% CI)	-0.271 (-0.875 to 0.332)*	0.214 (-0.384 to 0.812)*	-0.036 (-0.510 to 0.439)*
	P-value	0.459	0.555	0.901
	Reduction in cognitive decline vs. PBO	NR	NR	NR
ADAS-Cog14 Score	N	33	34	61
	LS Mean Change (SE)	5.574 (1.28)	5.746 (1.28)	4.506 (0.96)
	Diff (95% CI)	0.672 (-1.586 to 2.930)*	0.844 (-1.422 to 3.111)*	-0.395 (-2.192 to 1.401)*
	P-value	0.624	0.539	0.717
	Reduction in cognitive decline vs. PBO			
	Percent improvement vs. placebo	NR	NR	NR
ADCOMS	Timepoint	12 months		
	N	38	42	67
	LS Mean Change (SE)	0.158 (0.03)	0.149 (0.03)	0.139 (0.20)
	Diff (90% CI)	0.028 (-0.020 to 0.076)	0.019 (-0.029 to 0.066)	0.008 (-0.030 to 0.046)
	P-value	0.336	0.514	0.731
	Reduction in clinical decline vs. PBO	NR	NR	NR
	Timepoint	18 months		
	N	33	35	61
	LS Mean Change (SE)	0.173 (0.04)	0.192 (0.04)	0.199 (0.03)
	Diff (90% CI)	-0.202 (-0.083 to 0.042)	-0.001 (-0.064 to 0.061)	0.006 (-0.044 to 0.055)

	P-value	0.592	0.971	0.855
	Percent improvement vs. placebo	NR	NR	NR
	Reduction in cognitive decline vs. PBO	NR	NR	NR
Amyloid Outcomes (SUVr)				
	N	23	23	24
	Adjusted Mean Change	-0.094	-0.131	-0.197
	Difference in Mean Change (SD)	-0.099	-0.136	-0.201
	95% CI	NR	NR	NR
	P-Value	NR	NR	NR
MRI Outcomes				
Volumetric MRI: Whole Brain	N	32	38	55
	LS Mean Change (SE)	-26987.11 (1805.22)	-27972.21 (1706.45)	-26520.54 (1413.53)
	Diff (95% CI)	-5211.254 (-8291.455 to -2131.053)*	-6196.353 (-9115.840 to -3276.866)*	-4744.689 (-7242.988 to -2246.390)*
	P-value (Dunnett p-value)	0.005 (0.093)	0.001 (0.009)	0.002 (0.032)
Volumetric MRI: Ventricular Volume	N	34	39	55
	LS Mean Change (SE)	6250.43 (469.844)	7265.785 (445.381)	6338.779 (373.274)
	Diff (95% CI)	905.926 (103.475 to 1708.377)*	1921.281 (1157.356 to 2685.206)*	994.276 (334.281 to 1654.271)*
	P-value (Dunnett p-value)	0.063 (0.690)	0.001 (0.001)	0.013 (0.213)
Volumetric MRI: Hippocampus volume	N	34	39	55
	LS Mean Change (SE)	-305.254 (20.161)	-304.600 (19.053)	-297.469 (15.955)
	Diff (95% CI)	-47.958 (-82.366 to -13.549)*	-47.304 (-79.974 to -14.634)*	-40.173 (-68.411 to -11.934)*
	P-value (Dunnett p-value)	0.022 (0.328)	0.017 (0.269)	0.019 (0.296)

AD: Alzheimer's disease, ADCOMS: AD Composite Score, ADAS-Cog14: Alzheimer's Disease Assessment Scale – Cognitive Subscale 14-item, CDR-SB: Clinical Dementia Rating – Sum of Boxes, CI: confidence interval, LS; least squares, LCB: lecanemab, mg/kg: milligrams per kilogram, MRI: magnetic resonance imaging N: number, NR: not reported, PBO: placebo, REF: reference, SD: standard error, SE: standard error

*90% CI

Table D3.6 Lecanemab OLE Outcomes

Trial		G000-201 OLE	
Source		**McDade et al. 2022[100]; Swanson et al. CTAD conference 2021; Swanson et al. 2020[105]; Swanson et al. 2021 Neurology; Swanson et al. CTAD conference 2021[92,96,97]**	
Study Arms		Core phase lecanemab 10mg/kg Q2W*	Core placebo-treated*
Baseline N		38	45
Cognitive Outcomes			
ADCOMS	Timepoint	Core baseline to OLE baseline	
	N	30	40
	LS Mean Change (SE)	0.18	0.28
	P-value	p<0.05	p<0.05
	Timepoint	OLE baseline to 18 months	
	N	21	28
	LS Mean Change (SE)	0.3	0.4
CDR-SB	Timepoint	Core baseline to OLE baseline	
	N	31	40
	LS Mean Change (SE)	1.14	1.8
	Timepoint	OLE baseline to 18 months	
	N	24	29
	LS Mean Change (SE)	2.4	3.2
ADAS-Cog14	Timepoint	Core baseline to OLE baseline	
	N	28	40
	LS Mean Change (SE)	9.54	14.06
	Timepoint	OLE baseline to 18 months	
	N	22	26
	LS Mean Change (SE)	14.1	20.2
Amyloid Outcomes			
Florbetapir PET SUVr	Timepoint	Core baseline to OLE baseline	
	N	12	16
	Adjusted Mean Change	-0.26	0

	Timepoint	OLE baseline to 12 Months	
	N	17	15
	Adjusted Mean Change	-0.08	-0.23
Amyloid Visual Read	Timepoint	NR	3 months
	Amyloid negative, n(%)	NR	3 (43)
	Timepoint	NR	6 months
	Amyloid negative, n(%)	NR	6 (75)
	Timepoint	NR	12 months
	Amyloid negative, n(%)	NR	10 (83)
	Timepoint	NR	24 months
	Amyloid negative, n(%)	NR	4 (80)
CSF Outcomes			
Plasma Aβ42/40 Ratio	Timepoint	Core baseline to OLE baseline	
	N	25	32
	Adjusted Mean Change	0.55	-0.15
	Timepoint	Core baseline to OLE 12 months	
	N	25	31
	Adjusted Mean Change	0.007	0.008
Plasma P-tau, pg/ml	Timepoint	Core baseline to OLE baseline	
	N	20	27
	Adjusted Mean Change	-0.4	0.2
	Timepoint	Core baseline to OLE 12 months	
	N	20	25
	LS Mean Change	-1.06	-1.17

Aβ: beta-amyloid, ADCOMS: AD Composite Score, CI: confidence interval, CSF: cerebrospinal fluid, LS: least squares, mg/kg: milligram per kilogram, N: number, NR: not reported, OLE: open-label extension, PET: Positron Emission Tomography, p-tau: phosphorylated tau, Q2W: every two weeks, Q4W: Every four weeks, SE: standard error, SD: standard deviation, pg/ml: picograms per milliliter, SUVr: standardized uptake value ratio, t-tau: total tau

*Arms based upon the core study allocation

Table D3.7 Lecanemab Bayesian Analysis – ADCOMS Primary Analysis[92]

Lecanemab	Total N	ADCOMS - Primary Analysis								
		Δ from Baseline			Diff from Control		Posterior Quantities			
		Mean	SD	95% CI	Mean	95% CI	PR (Max)	Pr (ED90)	Pr SUP	Pr (CSD)
	Timepoint	12 months								
All Participants										
PBO	229	0.113	0.012	NR	NR	NR	--	--	--	--
2.5 mg/kg Q2W	51	0.134	0.024	NR	NR	NR	0.009	0.009	0.216	0.028
5 mg/kg Q4W	48	0.119	0.021	NR	NR	NR	0.022	0.031	0.416	0.07
5 mg/kg Q2W	87	0.116	0.016	NR	NR	NR	0.01	0.01	0.4467	0.053
10 mg/kg Q4W	242	0.084	0.011	NR	NR	NR	0.318	0.386	0.961	0.479
10 mg/kg Q2W	143	0.077	0.014	NR	NR	NR	0.642	0.563	0.976	0.638

ADCOMS: AD Composite Score, ApoE: Apolipoprotein E, CI: confidence interval, CSD: clinically significant difference (25% better than placebo), Diff: difference, ED90: dose regimen with at least 90% of the dmax treatment effect, Max: maximum treatment effect, mg/kg: milligram per kilogram, NR: not reported, PBO: placebo, Pr: probability, Pr (Max): probability of being maximal effective dose, Pr (ED90): probability of being the ED90 dose, Pr SUP: probability to be superior to placebo by any magnitude, Pr (CSD): probability to be better than placebo by at least 25%, Q2W: every two weeks, Q4W: Every four weeks, SD: standard deviation, Δ: change

Table D3.8 Lecanemab Bayesian Analysis – ADCOMS Secondary Analysis[92]

Lecanemab	Total N	ADCOMS - Secondary Analysis								
		Δ from Baseline			Diff from Control		Posterior Quantities			
		Mean	SD	95% CI	Mean	95% CI	PR (Max)	Pr (ED90)	Pr SUP	Pr (CSD)
	Timepoint	18 months								
All Participants										
PBO	238	0.172	NR	0.142 to 0.202	REF	REF	--	--	--	--
2.5 mg/kg Q2W	52	0.156	NR	0.101 to 0.210	-0.017	-0.079 to 0.045	0.128	0.138	0.702	0.333
5 mg/kg Q4W	48	0.156	NR	0.108 to 0.206	-0.016	-0.073 to 0.041	0.097	0.129	0.719	0.32
5 mg/kg Q2W	89	0.165	NR	0.127 to 0.205	-0.007	-0,056 to 0.043	0.018	0.019	0.622	0.183
10 mg/kg Q4W	246	0.142	NR	0.113 to 0.171	-0.031	-0.072 to 0.011	0.155	0.194	0.927	0.513
10 mg/kg Q2W	152	0.126	NR	0.090 to 0.160	-0.047	-0.093 to -0.001	0.603	0.52	0.977	0.76
ApoE ε4 Carriers										
PBO	168	0.18	NR	0.144 to 0.216	REF	REF	--	--	--	--
2.5 mg/kg Q2W	38	0.149	NR	0.085 to 0.213	-0.031	-0.105 to 0.042	0.09	0.106	0.804	0.515
5 mg/kg Q4W	37	0.155	NR	0.098 to 0.214	-0.026	-0.092 to 0.043	0.048	0.072	0.778	0.452
5 mg/kg Q2W	81	0.158	NR	0.116 to 0.202	-0.023	-0.078 to 0.034	0.012	0.013	0.789	0.4
10 mg/kg Q4W	218	0.139	NR	0.108 to 0.171	-0.041	-0.089 to 0.006	0.058	0.08	0.956	0.679
10 mg/kg Q2W	45	0.096	NR	0.027 to 0.154	-0.084	-0.161 to -0.015	0.792	0.728	0.992	0.936

ApoE ε4 non-carriers										
PBO	70	0.146	NR	0.092 to 0.201	REF	REF	--	--	--	--
2.5 mg/kg Q2W	14	0.154	NR	0.068 to 0.243	0.008	-0.094 to 0.111	0.209	0.209	0.442	0.23
5 mg/kg Q4W	11	0.149	NR	0.074 to 0.226	0.002	-0.090 to 0.096	0.191	0.215	0.481	0.241
5 mg/kg Q2W	8	0.161	NR	0.092 to 0.245	0.014	-0.074 to 0.113	0.082	0.076	0.386	0.166
10 mg/kg Q4W	28	0.143	NR	0.082 to 0.205	-0.003	-0.085 to 0.079	0.218	0.226	0.531	0.257
10 mg/kg Q2W	107	0.135	NR	0.095 to 0.174	-0.011	-0.079 to 0.056	0.3	0.274	0.63	0.29

ADCOMS: AD Composite Score, ApoE: Apolipoprotein E, CI: confidence interval, CSD: clinically significant difference (25% better than placebo), Diff: difference, ED90: dose regimen with at least 90% of the dmax treatment effect, Max: maximum treatment effect, mg/kg: milligram per kilogram, NR: not reported, PBO: placebo, Pr: probability, Pr (Max): probability of being maximal effective dose, Pr (ED90): probability of being the ED90 dose, Pr SUP: probability to be superior to placebo by any magnitude, Pr (CSD): probability to be better than placebo by at least 25%, Q2W: every two weeks, Q4W: Every four weeks, SD: standard deviation, Δ: change

Table D3.9 Lecanemab Bayesian Analysis – CDR-SB[92]

Lecanemab	**Total N**	**CDR-SB**								
		Δ from Baseline			**Diff from Control**		**Posterior Quantities**			
		Mean	SD	95% CI	Mean	95% CI	PR (Max)	Pr (ED90)	Pr SUP	Pr (CSD)
	18 months									
All Participants										
PBO	238	1.248	NR	0.952 to 1.543	REF	REF	--	--	--	NR
2.5 mg/kg Q2W	52	1.053	NR	0.520 to 1.579	-0.195	-0.802 to 0.404	0.176	0.183	0.74	NR
5 mg/kg Q4W	48	1.25	NR	0.783 to 1.777	0.002	-0.552 to 0.602	0.031	0.046	0.509	NR
5 mg/kg Q2W	89	1.157	NR	0.793 to 1.547	-0.09	-0.560 to 0.394	0.028	0.027	0.65	NR
10 mg/kg Q4W	246	0.923	NR	0.637 to 1.206	-0.325	-0.733 to 0.083	0.245	0.304	0.941	NR
10 mg/kg Q2W	152	0.835	NR	0.481 to 1.174	-0.413	-0.870 to 0.038	0.52	0.44	0.964	NR
ApoE ε4 Carriers										
PBO	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
2.5 mg/kg Q2W	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
5 mg/kg Q4W	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR

5 mg/kg Q2W	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
10 mg/kg Q4W	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
10 mg/kg Q2W	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
ApoE ε4 non-carriers										
PBO	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
2.5 mg/kg Q2W	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
5 mg/kg Q4W	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
5 mg/kg Q2W	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
10 mg/kg Q4W	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
10 mg/kg Q2W	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR

ApoE: Apolipoprotein E, CDR-SB: Clinical Dementia Rating – Sum of Boxes, CI: confidence interval, CSD: clinically significant difference (25% better than placebo), Diff: difference, ED90: dose regimen with at least 90% of the dmax treatment effect, Max: maximum treatment effect, mg/kg: milligram per kilogram, NR: not reported, PBO: placebo, Pr: probability, Pr (Max): probability of being maximal effective dose, Pr (ED90): probability of being the ED90 dose, Pr SUP: probability to be superior to placebo by any magnitude, Pr (CSD): probability to be better than placebo by at least 25%, Q2W: every two weeks, Q4W: Every four weeks, SD: standard deviation, Δ: change

Table D3.10 Lecanemab Bayesian Analysis – ADAS-Cog14[92]

Lecanemab	**Total N**	**ADAS-Cog14**								
		Δ from Baseline			**Diff from Control**		**Posterior Quantities**			
		Mean	SD	95% CI	Mean	95% CI	PR (Max)	Pr (ED90)	Pr SUP	Pr (CSD)
	18 months									
All Participants										
PBO	237	3.632	NR	2.501 to 4.766	REF	REF	--	--	--	NR
2.5 mg/kg Q2W	52	3.857	NR	1.748 to 6.007	0.225	-2.164 to 2.333	0.03	0.038	0.428	NR
5 mg/kg Q4W	47	3.859	NR	1.910 to 5.921	0.228	-2.030 to 2.333	0.022	0.031	0.426	NR
5 mg/kg Q2W	89	3.221	NR	1.711 to 4.750	-0.411	-2.299 to 1.483	0.037	0.046	0.668	NR
10 mg/kg Q4W	246	2.91	NR	1.808 to 4.016	-0.721	-2.296 to 0.855	0.049	0.068	0.817	NR
10 mg/kg Q2W	152	1.611	NR	0.234 to 2.952	-2.021	-3.795 to -0.273	0.861	0.817	0.988	NR
ApoE ε4 Carriers										
PBO	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
2.5 mg/kg Q2W	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR

5 mg/kg Q4W	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
5 mg/kg Q2W	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
10 mg/kg Q4W	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
10 mg/kg Q2W	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
ApoE ε4 non-carriers										
PBO	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
2.5 mg/kg Q2W	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
5 mg/kg Q4W	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
5 mg/kg Q2W	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
10 mg/kg Q4W	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
10 mg/kg Q2W	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR

ADAS-Cog14: Alzheimer's Disease Assessment Scale – Cognitive Subscale 14-item, ApoE: Apolipoprotein E, CI: confidence interval, CSD: clinically significant difference (25% better than placebo), Diff: difference, ED90: dose regimen with at least 90% of the dmax treatment effect, Max: maximum treatment effect, mg/kg: milligram per kilogram, NR: not reported, PBO: placebo, Pr: probability, Pr (Max): probability of being maximal effective dose, Pr (ED90): probability of being the ED90 dose, Pr SUP: probability to be superior to placebo by any magnitude, Pr (CSD): probability to be better than placebo by at least 25%, Q2W: every two weeks, Q4W: Every four weeks, SD: standard deviation, Δ: change

Table D3.11 Safety

Trial	**G000-201**						**CLARITY AD**	
Source	**Swanson et al. 2021[92]; Landry 2022[96]; CTAD conference 2022[35]**						**van Dyck et al., 2022[35]; Sabbagh et al. CTAD conference 2022[106], Piller, C.[107]**	
Study Arms	2.5 mg/kg biweekly	5 mg/kg monthly	5 mg/kg biweekly	10 mg/kg monthly	10 mg/kg biweekly	Placebo	10 mg/kg biweekly	Placebo
N	52	51	92	253	161	245	898*	897
Adverse Events								
Any adverse event	46 (88.5)	48 (94.1)	81 (88.0)	238 (94.1)	139 (86.3)	216 (88.2)	798 (88.9)	735 (81.9)
Treatment-related TEAE	23 (44.2)	25 (49.0)	31 (33.7)	135 (53.4)	76 (47.2)	65 (26.5)	798 (88.9)	735 (81.9)
Death	2 (3.8)	0 (0)	1 (1.1)	2 (0.8)	0 (0)	2 (0.8)	6 (0.7)	7 (0.8)
ARIA-E Leading to death	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	3†	NR

ARIA-H Leading to death	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)		NR
Serious adverse event	10 (19.2)	4 (7.8)	16 (17.4)	31 (12.3)	25 (15.5)	43 (17.6)	126 (14.0)	101 (11.3)
AE leading to D/C of treatment	NR	NR	NR	NR	NR	NR	62 (6.9)	26 (2.9)
Infusion-related reaction leading to D/C of treatment	NR	NR	NR	NR	2.50%	0.80%	NR	NR
AE leading to D/C of trial	7 (13.5)‡	4 (7.8)	10 (10.9)	47 (18.6)	24 (14.9)	15 (6.1)	51 (5.7)	28 (3.1)
ARIA-E leading to D/C	1/52 (1.9)	1/51 (2.0)	3/92 (3.3)	25/253 (9.9)	16/161 (9.9)	NR	NR	NR
Other Adverse Events								
Infusion-related reaction	5.80%	7.80%	12.00%	22.90%	19.90%	3.30%	237 (26.4)§	66 (7.4)
Infusion-related reaction (Grade 1 or 2)	NR	NR	NR	NR	NR	NR	96%	
Infusion-related reaction (First dose)	NR	NR	NR	NR	NR	NR	75%	
Fall	NR	NR	NR	NR	NR	NR	93 (10.4)	86 (9.6)
Dizziness	NR	NR	NR	NR	NR	NR	49 (5.5)	46 (5.1)
Headache	NR	NR	NR	NR	NR	NR	100 (11.1)	73 (8.1)
Superficial siderosis of CNS	NR	NR	NR	NR	NR	NR	50 (5.6)	22 (2.5)
Arthralgia	NR	NR	NR	NR	NR	NR	53 (5.9)	62 (6.9)
UTI	NR	NR	NR	NR	NR	NR	78 (8.7)	82 (9.1)
Diarrhea	NR	NR	NR	NR	NR	NR	48 (5.3)	58 (6.5)
Anxiety	NR	NR	NR	NR	NR	NR	45 (5.0)	38 (4.2)
Back pain	NR	NR	NR	NR	NR	NR	60 (6.7)	52 (5.8)
COVID-19	NR	NR	NR	NR	NR	NR	64 (7.1)	60 (6.7)
Anti-drug antibodies (ADA)	NR	NR	NR	NR	40.90%	NA	NR	NR
NAb Positive	NR	NR	NR	NR	25.40%	NA	NR	NR
Serious AEs								
Infusion-related reactions	NR	NR	NR	NR	NR	NR	11 (1.2)	0
ARIA-E	NR	NR	NR	NR	NR	NR	7 (0.8)	0
ARIA-H	NR	NR	NR	NR	NR	NR	5 (0.6)	1 (0.1)
Serious AEs without ARIA or infusion-related reactions	NR	NR	NR	NR	NR	NR	111 (12.4)	101 (11.3)

ARIA Events									
ARIA-E	Any	1/52 (1.9)	1/51 (2.0)	3/92 (3.3)	25/253 (9.9)	16/161 (9.9)	2/245 (0.8)	113 (12.6)	15 (1.7)
	APOE4 positive	1/1 (100)	1/1 (100)	3/3 (100)	23/25 (92)	7/16 (44)	2/2 (100)	98/620 (15.8)	14/611 (2.3)
	APOE4 positive heterozygote	NR	NR	NR	NR	NR	NR	52/479 (10.9)	9/478 (1.9)
	APOE4 positive homozygote	NR	NR	NR	NR	NR	NR	46/141 (32.6)	5/133 (3/8)
	APOE4 negative	0/112 (0)	0/112 (0)	0/112 (0)	0/112 (0)	2/112 (7.1)	9/112 (8.0)	15/278 (5.4)	1/286 (0.3)
	Recurrent ARIA-E	NR	NR	NR	NR	NR	NR	28 (3.1)	1 (0.1)
	Radiographic severity: mild	NR	NR	NR	NR	NR	NR	37	9
	Radiographic severity: moderate	NR	NR	NR	NR	NR	NR	66	6
	Radiographic severity: severe	NR	NR	NR	NR	NR	NR	9	0
	Clinical severity: mild	NR	NR	NR	NR	NR	NR	10	NA
	Clinical severity: moderate	NR	NR	NR	NR	NR	NR	12	NA
	Clinical severity: severe	NR	NR	NR	NR	NR	NR	3	NA
	Median time to complete resolution of ARIA-E	NR	NR	NR	NR	NR	NR	81% resolution within 4 months; 64% by 90 days; 81% by 120 days; 92% by 6 months with lecanemab.**	NR
Symptomatic ARIA-E	Symptomatic	1 (1.9)	0 (0)	1 (1.1)	1 (0.4)	2 (1.2)	NR	25 (2.8)#	0
	Symptomatic: APOE4 positive	NR	NR	NR	NR	NR	NR	21/620 (3.4)	0/611
	Symptomatic: APOE4 positive heterozygote	NR	NR	NR	NR	NR	NR	8/479 (1.7)	0/478

	Symptomatic: APOE4 positive homozygote	NR	NR	NR	NR	NR	NR	13/141 (9.2)	0/133
	Symptomatic: APOE4 negative	NR	NR	NR	NR	NR	NR	4/278 (1.4)	0/286
ARIA-H, n(%)	Any	2 (3.8)	7 (13.7)	17 (18.5)	28 (11.1)	11 (6.8)	13 (5.3)	155 (17.3)¤	81 (9.0)
	Microhemorrhage	NR	NR	NR	NR	NR	NR	126 (14.0)	68 (7.6)
	Superficial siderosis	NR	NR	NR	NR	NR	NR	50 (5.6)	21 (2.3)
	Macrohemorrhage	NR	NR	NR	NR	1/161 (0.6)	0/245 (0)	5 (0.6)	1 (0.1)
	APOE4 positive	57/436 (13.1)**					NR	122/620 (19.7)	69/611 (11.3)
	APOE4 positive heterozygote	NR	NR	NR	NR	NR	NR	67/479 (14.0)	41/478 (8.6)
	APOE4 positive homozygote	NR	NR	NR	NR	NR	NR	55/141 (39.0)	28 (133 (21.1)
	APOE4 negative	8/173 (4.6)**					NR	33/278 (11.9)	12/286 (4.2)
	Symptomatic	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	6 (0.7)	2 (0.2)
Cerebral macrohemorrhage		NR	NR	NR	NR	NR	NR	6 (0.7)	2 (0.2)
Deaths with cerebral macrohemorrhage		NR	NR	NR	NR	NR	NR	0	1/897 (0.1)
ARIA-E or ARIA-H		NR	NR	NR	NR	NR	NR	193 (21.5)	85 (9.5)
ARIA-E with ARIA-H		0 (0)	1 (2.0)	1 (1.1)	13 (5.1)	7 (4.3)	1 (0.4)	74 (8.2)	9 (1.0)
ARIA-H without ARIA-E		NR	NR	NR	NR	NR	NR	80 (8.9)	70 (7.8)

AE: adverse event, ADU: aducanumab, ApoE: Apolipoprotein E, ARIA-E: amyloid-related imaging abnormalities due to edema/effusion, ARIA-H: amyloid-related imaging abnormalities due to hemorrhage or superficial siderosis, CNS: central nervous system, D/C: discontinuation, mg/kg: milligram per kilogram, NA: not applicable, NAb: neutralizing antibody, NR: not reported, PBO: placebo, TEAE: treatment-emergent adverse events, URTI: upper respiratory tract infection, UTI: Urinary tract infection

*Safety population

†Reported in the core and OLE phase.[43-46]

‡Reporting of these values was inconsistent in manuscript and supplement. We report values from the main report.

§56% of the participants did not take preventative medications (i.e., nonsteroidal anti-inflammatory drugs, antihistamines, or glucocorticoids) for infusion-related reactions.

#Symptoms were headache, visual disturbance, and confusion.

¤Timing of ARIA-H occurred randomly during treatment course, but ARIA-H with ARIA-E occurred early.

**Across all lecanemab doses.

Table D3.12 Additional Safety

Trial		Lecanemab: Phase 1- SC	
Source		**Rawal et al. 2022[102]**	
Study Arms		**IV infusion**	**SC injection**
N		30	29
Treatment-related TEAE		0.03%	0.07%
Injection-site reaction		NA	20.70%
Infusion-related reaction (Grade 1 or 2)		33.30%	
Anti-drug antibodies (ADA)		0.03%	0.07%
Trial		**G000-201 OLE**	
Source		**Landry 2022; Reyderman et al. 2022[99,108]**	
Study Arms		**10 mg/kg biweekly**	**Core placebo-treated**
Infusion-related reaction		20.60%	
Anti-drug antibodies (ADA)		6.10%	NA
NAb Positive		0.00%	NA
ARIA-E	Any	7.80%	8.90%
	ApoE ε4 positive	NR	4/33 (12.1%)*
	ApoE ε4 negative	NR	0/14 (0%)
ARIA-H	Macrohemorrhage	1/180 (0.6)	NA

ApoE: Apolipoprotein E, ARIA-E: amyloid-related imaging abnormalities due to edema/effusion, ARIA-H: amyloid-related imaging abnormalities due to hemorrhage or superficial siderosis, IV: intravenous, N: number, NA: not applicable, NR: not reported, NAb: neutralizing antibody, SC: subcutaneous, TEAE: treatment-emergent adverse event

*ApoE ε4 and core placebo-treated participants. 25% homozygous and 11.1% heterozygous.

Table D3.13 Subgroup Data – Lecanemab Phase II ADCOMS by Disease Severity

Trial	Timepoint	Study Arms	Subgroups	ADCOMS			
				n/N	LSM (SE)	LSM Diff (90% CI)	P-Value
Lecanemab							
G000-201 (MMRM Analysis)[92]	18 months	2.5 mg/kg Q2W	MCI Due to AD	22/52	0.106 (0.037)	-0.062 (-0.128 to 0.004)	0.12
			Mild AD	11/52	0.3 (0.075)	0.069 (-0.066 to 0.205)	0.397
		5 mg/kg Q4W	MCI Due to AD	30/48	0.154 (0.034)	-0.014 (-0.076 to 0.047)	0.7
			Mild AD	5/48	0.297 (0.092)	0.067 (-0.095 to 0.229)	0.493
		5 mg/kg Q2W	MCI Due to AD	37/89	0.16 (0.029)	0.008 (-0.063 to 0.046)	0.8
			Mild AD	24/89	0.248 (0.052)	0.018 (-0.084 to 0.119)	0.776
		10 mg/kg Q4W	MCI Due to AD	101/246	0.14 (0.019)	0.029 (-0.068 to 0.010)	0.227
			Mild AD	45/246	0.205 (0.039)	-0.026 (-0.109 to 0.058)	0.615
		10 mg/kg Q2W	MCI Due to AD	47/152	0.113 (0.025)	-0.056 (-0.105 to -0.007)	0.058
			Mild AD	32/152	0.149 (0.043)	-0.081 (-0.171 to 0.009)	0.14
		PBO	MCI Due to AD	111/238	0.169 (0.018)	REF	REF
			Mild AD	49/238	0.23 (0.036)	REF	REF

AD: Alzheimer's disease, ADCOMS: AD Composite Score, Diff: difference, LSM: least squares mean, MCI: mild cognitive impairment, mg/kg: milligram per kilogram, n/N: number/ total number, PBO: placebo, Q2W: every two weeks, Q4W: every four weeks, REF: reference, SE: standard error

Table D3.14 Subgroup Data – Lecanemab Phase II CDR-SB by Disease Severity

Trial	Timepoint	Study Arms	Subgroups	CDR-SB			
				n/N	LSM (SE)	LSM Diff (90% CI)	P-Value
Lecanemab							
G000-201 (MMRM Analysis)[92]	18 months	2.5 mg/kg Q2W	MCI Due to AD	23/52	0.757 (0.341)	-0.411 (-1.014 to 0.192)	0.262
			Mild AD	11/52	2.242 (0.740)	0.117 (-1.224 to 1.458)	0.885
		5 mg/kg Q4W	MCI Due to AD	30/48	1.402 (0.313)	0.233 (-0.331 to 0.798)	0.496
			Mild AD	6/48	2.634 (0.887)	0.509 (-1.054 to 2.072)	0.591
		5 mg/kg Q2W	MCI Due to AD	39/89	1.08 (0.266)	-0.089 (-0.585 to 0.408)	0.769
			Mild AD	28/89	1.948 (0.500)	-0.177 (-1.166 to 0.812)	0.768

		10 mg/kg Q4W	MCI Due to AD	101/246	1.072 (0.171)	-0.096 (-0.455 to 0.262)	0.658
			Mild AD	48/246	1.578 (0.377)	-0.547 (-1.373 to 0.280)	0.275
		10 mg/kg Q2W	MCI Due to AD	49/152	1.01 (0.230)	-0.159 (-0.603 to 0.286)	0.557
			Mild AD	35/152	1.042 (0.416)	-1.083 (-1.967 to -0.198)	0.044
		PBO	MCI Due to AD	112/238	1.168 (0.162)	REF	REF
			Mild AD	49/238	2.125 (0.354)	REF	REF

AD: Alzheimer's disease, CDR-SB: Clinical Dementia Rating – Sum of Boxes, Diff: difference, LSM: least squares mean, MCI: mild cognitive impairment, mg/kg: milligram per kilogram, n/N: number/ total number, PBO: placebo, Q2W: every two weeks, Q4W: every four weeks, REF: reference, SE: standard error

Table D3.15 Subgroup Data – Lecanemab Phase II ADAS-Cog14 by Disease Severity

Trial	Timepoint	Study Arms	Subgroups	ADAS-Cog14			
				n/N	LSM (SE)	LSM Diff (90% CI)	P-Value
Lecanemab							
G000-201 (MMRM Analysis)[92]	18 months	2.5 mg/kg Q2W	MCI Due to AD	22/52	3.572 (1.428)	-1.061 (-3.571 to 1.450)	0.486
			Mild AD	11/52	9.443 (2.469)	4.083 (-0.367 to 8.532)	0.131
		5 mg/kg Q4W	MCI Due to AD	29/48	5.168 (1.331)	0.535 (-1.840 to 2.910)	0.719
			Mild AD	5/48	6.72 (3.054)	1.360 (-3.980 to 6.699)	0.675
		5 mg/kg Q2W	MCI Due to AD	37/89	4.042 (1.119)	-0.591 (-2.659 to 1.477)	0.638
			Mild AD	24/89	4.891 (1.734)	-0.469 (-3.825 to 2.886)	0.817
		10 mg/kg Q4W	MCI Due to AD	101/246	3.63 (0.722)	1.002 (-2.486 to 0.482)	0.266
			Mild AD	45/246	6.424 (1.294)	1.053 (-1.699 to 3.825)	0.525
		10 mg/kg Q2W	MCI Due to AD	47/152	1.925 (0.968)	-2.707 (-4.559 to -0.855)	0.016
			Mild AD	32/152	3.172 (1.426)	-2.188 (-5.170 to 0.793)	0.227
		PBO	MCI Due to AD	112/238	4.633 (0.684)	REF	REF
			Mild AD	46/238	5.36 (1.216)	REF	REF

ADAS-Cog14: Alzheimer's Disease Assessment Scale – Cognitive Subscale 14-item, AD: Alzheimer's disease, Diff: difference, LSM: least squares mean, MCI: mild cognitive impairment, mg/kg: milligram per kilogram, n/N: number/ total number, PBO: placebo, Q2W: every two weeks, Q4W: every four weeks, REF: reference, SE: standard error

Table D3.16 Subgroup Data – CLARITY AD Tau Pathology by Brain Region

Trial	Brain Region	N placebo, N Lecanemab	Adjusted Mean Difference in Tau Pathology	P value
CLARITY AD (CTAD conference 2022)[42]	Medial temporal	122, 135	-0.068	0.0024
	Meta temporal	122, 135	-0.071	0.012
	Temporal	132, 136	-0.065	0.016
	Frontal	122, 135	-0.023	0.22
	Cingulate	132, 135	-0.034	0.13
	Parietal	122, 135	-0.029	0.25
	Occipital	132, 135	-0.003	0.91
	Whole cortical gray matter	122, 443	-0.035	0.1

CTAD: Clinical trials on Alzheimer's Disease, N: number

Table D3.17 Subgroup Data – CLARITY AD CDR-SB by Comorbidities and Anticoagulant Use

Trial	Comorbidities and Anticoagulant Use	N Placebo, N Lecanemab	CDR-SB Placebo Decline	Difference vs. Placebo	% Slowing
CLARITY AD (Cohen et al. CTAD conference 2022)	Overall	875, 859	1.66	-0.45	27
	Hypertension	486, 471	1.56	-0.47	30
	Diabetes	130, 130	1.75	-0.58	33
	Heart disease	131, 142	1.7	-0.88	52
	Hypercholesterolemia	518, 533	1.75	-0.55	32
	Obesity	136, 145	1.38	-0.53	38
	Anticoagulants	72, 80	2.07	-0.74	36

CTAD: Clinical trials on Alzheimer's Disease, CDR-SB: Clinical Dementia Rating – Sum of Boxes, %: percent, N: number

Table D3.18 Subgroup Data – CLARITY AD CDR-SB at 18 months by Various Subgroups[35]

Trial	Subgroups		Adjusted Mean Difference in CDR-SB at 18 months	% Slowing	N Placebo, N Lecanemab
CLARITY AD (van Dyck et al. 2022)	Use of symptomatic AD medication at baseline	Yes	-0.48	25	468, 447
		No	-0.39	28	407, 412
	Clinical subgroup	MCI	-0.35	28	544, 528
		Mild AD	-0.62	27	331, 331
	ApoE ε4 status	Carrier	-0.33	21	600, 592
		Non carrier	-0.75	41	275, 267
	Region	North America	-0.52	34	516, 514
		Asia	-0.33	25	146, 141
		Europe	-0.33	14	213, 204
	ApoE ε4 genotype status	Non-carrier	-0.75	41	275, 267
		Heterozygote	-0.5	30	468, 456
		Homozygote	0.28	-22	132, 136
	Sex	Female	-0.2	12	464, 443
		Male	-0.73	43	411, 416

	Age	<65	-0.08	6	178, 166
		65-74	-0.37	23	381, 368
		≥75	-0.72	40	316, 325
	Ethnicity	Hispanic	-0.5	52	108, 107
		Non-Hispanic	-0.46	25	743, 715
	Race	White	-0.49	27	677, 655
		Asian	-0.35	19	148, 147
		Black	-0.72	63	24, 20
	Ethnicity - USA	Hispanic	-0.53	113	99, 100
		Non-Hispanic	-0.58	31	356, 354
	Race - USA	White	-0.58	36	431, 431
		Black	-0.55	63	21, 19

AD: Alzheimer's disease, ApoE: Apolipoprotein E, CDR-SB: Clinical Dementia Rating – Sum of Boxes, MCI: mild cognitive impairment, N: number, USA: United States of America

Table D3.19 Subgroup Data – CLARITY AD ADAS-Cog14 at 18 months by Various Subgroups[35]

Trial	Subgroups		Adjusted Mean Difference in ADAS-Cog14 at 18 months	% Slowing	N Placebo, N Lecanemab
CLARITY AD (van Dyck et al. 2022)	Use of symptomatic AD medication at baseline	Yes	-2.06	29	466, 445
		No	-0.64	16	406, 409
	Clinical subgroup	MCI	-0.93	23	542, 525
		Mild AD	-2.46	30	330, 329
	ApoE ε4 status	Carrier	-1.11	21	599, 588
		Non carrier	-2.19	35	273, 266
	Region	North America	-1.43	31	514, 512
		Asia	-1.38	25	146, 140
		Europe	-1.71	22	212, 202
	ApoE ε4 genotype status	Non-carrier	-2.19	35	273, 266
		Heterozygote	-1.28	23	467, 453

		Homozygote	-0.53	13	132, 135
	Sex	Female	-0.98	18	462, 441
		Male	-1.97	34	410, 413
	Age	<65	-0.92	14	177, 165
		65-74	-1.47	29	380, 365
		≥75	-1.67	30	315, 324
	Ethnicity	Hispanic	-2.06	387	108, 107
		Non-Hispanic	-1.37	21	740, 711
	Race	White	-1.65	28	674, 652
		Asian	-1.46	25	148, 146
		Black	-1.59	280	24, 20
	Ethnicity - USA	Hispanic	-2.18	-222*	99, 100
		Non-Hispanic	-1.34	21	354, 353
	Race - USA	White	-1.65	33	429, 430
		Black	-1.00	209	21, 19

AD: Alzheimer's disease, ADAS-Cog14: Alzheimer's Disease Assessment Scale – Cognitive Subscale 14-item, ApoE: Apolipoprotein E, MCI: mild cognitive impairment, N: number, USA: United States of America

*A negative value represents improvement on this outcome measure.

Table D3.20 Subgroup Data – CLARITY AD ADCOMS at 18 months by Various Subgroups[35]

Trial	Subgroups		Adjusted Mean Difference in ADCOMS at 18 months	% Slowing	N Placebo, N Lecanemab
CLARITY AD (van Dyck et al. 2022)	Use of symptomatic AD medication at baseline	Yes	-0.058	23	468, 446
		No	-0.039	22	407, 411
	Clinical subgroup	MCI	-0.042	25	544, 527
		Mild AD	-0.067	23	331, 330
	ApoE ε4 status	Carrier	-0.041	20	600, 590
		Non carrier	-0.072	32	275, 267
	Region	North America	-0.048	26	516, 513
		Asia	-0.05	24	146, 141
		Europe	-0.049	17	213, 203

	ApoE ε4 genotype status	Non-carrier	-0.072	32	275, 267
		Heterozygote	-0.056	25	468, 454
		Homozygote	0.009	-5	132, 136
	Sex	Female	-0.022	10	464, 442
		Male	-0.082	38	411, 415
	Age	<65	-0.009	5	178, 166
		65-74	-0.049	25	381, 367
		≥75	-0.075	31	316, 324
	Ethnicity	Hispanic	-0.052	44	108, 107
		Non-Hispanic	-0.049	21	743, 714
	Race	White	-0.050	22	677, 654
		Asian	-0.053	19	148, 147
		Black	-0.041	30	24, 20
	Ethnicity - USA	Hispanic	-0.051	103	99, 100
		Non-Hispanic	-0.052	23	356, 353
	Race - USA	White	-0.054	28	431, 430
		Black	-0.019	20	21, 19

AD: Alzheimer's disease, ADCOMS: AD Composite Score, ApoE: Apolipoprotein E, MCI: mild cognitive impairment, N: number, USA: United States of America

Table D3.21 Subgroup Data – CLARITY AD ADCS-MCI-ADL at 18 months by Various Subgroups[35]

Trial	Subgroups		Adjusted Mean Difference in ADCS-MCI-ADL at 18 months	% Slowing	N Placebo, N Lecanemab
CLARITY AD (van Dyck et al. 2022)	Use of symptomatic AD medication at baseline	Yes	2.39	37	423, 404
		No	1.53	33	373, 379
	Clinical subgroup	MCI	1.64	38	499, 492
		Mild AD	2.71	38	297, 291
	ApoE ε4 status	Carrier	1.72	33	551, 549
		Non carrier	2.73	47	245, 234
	Region	North America	1.9	42	473, 473
		Asia	1.31	23	130, 121

		Europe	2.76	41	193, 189
	ApoE ε4 genotype status	Non-carrier	2.73	47	245, 234
		Heterozygote	1.97	36	430, 422
		Homozygote	1.03	25	121, 127
	Sex	Female	1.01	19	416, 399
		Male	3.17	54	380, 384
	Age	<65	1.28	26	166, 151
		65-74	2.02	38	356, 343
		>=75	1.48	40	274, 289
	Ethnicity	Hispanic	2.22	92	95, 95
		Non-Hispanic	1.98	33	677, 653
	Race	White	2.20	40	616, 604
		Asian	1.26	23	132, 127
		Black	1.08	184	22, 17
	Ethnicity - USA	Hispanic	1.92	318	86, 90
		Non-Hispanic	2.29	40	329, 325
	Race - USA	White	2.23	45	392, 395
		Black	1.5	-221*	20, 16

AD: Alzheimer's disease, ADCS-MCI-ADL: Alzheimer's Disease Cooperative Study – Activities of Daily Living Inventory (MCI version), ApoE: Apolipoprotein E, MCI: mild cognitive impairment, N: number, USA: United States of America.

*A negative value represents improvement on this outcome measure.

Table D3.22 Subgroup Data – CLARITY AD CDR-SB Sensitivity Analyses[47]

Trial	CDR-SB Sensitivity Analyses	Adjusted Mean Change from Baseline at 18 Months (Placebo)	Adjusted Mean Change from Baseline at 18 Months (Lecanemab)	Treatment Difference at 18 Months (95% CI), p value
CLARITY AD (CTAD conference 2022)	Rank ANCOVA with missing data imputed via mITT	NA	NA	-0.456 (95% CI: -0.737, -0.176), p<0.001
	MMRM repeated on all randomized subjects (ITT)	1.659	1.225	-0.434 (95% CI: -0.644, -0.224), p<0.001
	Primary MMRM repeated censoring assessments after ARIA-E	1.672	1.169	-0.503 (95% CI: -0.726, -0.279), p<0.001
	Primary MMRM repeated to evaluate the impact of COVID-19	1.603	1.208	-0.394 (95% CI: -0.613, -0.176), p<0.001

ARIA-E: amyloid-related imaging abnormalities due to edema/effusion, CDR-SB: Clinical Dementia Rating – Sum of Boxes, CI: confidence interval, ITT: intent-to-treat analysis, mITT: modified intent-to-treat analysis, MMRM: mixed models for repeated measure, NA: not applicable

Table D3.23 Subgroup Data – CLARITY AD CDR-SB Subdomains[41]

Trial	CDR-SB Subdomains	N Placebo, N Lecanemab	Adjusted Mean Difference	% Slowing	P value
CLARITY AD (Cohen et al. 2022 CTAD conference)	Memory	875, 859	-0.077	27.5	0.0012
	Orientation	875, 859	-0.081	28.1	0.0004
	Judgement/Problem Solving	875, 859	-0.053	23.6	0.01
	Community Affairs	875, 859	-0.07	21.2	0.005
	Home and Hobbies	875, 859	-0.098	28.8	0.0002
	Personal Care	875, 859	-0.067	29.9	0.013

CTAD: Clinical trials on Alzheimer's Disease, CDR-SB: Clinical Dementia Rating – Sum of Boxes, N: number, %: percent.

Table D3.24 Correlations

Trial		G000-201		
Source		**Swanson et al. CTAD 2021[96]**		
Study Arms		10 mg/kg monthly	10 mg/kg biweekly	Placebo
Baseline N		246	152	238
Correlations				
Change in ADCOMS vs. Change in PET SUVr at 18 Months (Population Level)	R	NR	0.832	NR
	P-value	NR	p=0.08	NR
Change in ADCOMS vs. Change in PET SUVr at 18 Months (Individual Level)	R	NR	0.199	NR
	P-value	NR	p=0.036	NR
Change in ADCOMS vs. Change in Plasma AB42/40 at 18 Months (Population Level)	R	NR	-0.306	NR
	P-value	NR	NS	NR
Change in ADCOMS vs. Change in Plasma AB42/40 at 18 Months (Individual Level)	R	NR	-0.208	NR
	P-value	NR	p=0.05	NR

ADCOMS: AD Composite Clinical Outcome, mg/kg: milligram / kilogram, NfL: neurofilament light, NR: not reported, NS: not significant, PBO: placebo, PET: Positron Emission Tomography, R: Regression coefficient, SUVr: Standardized uptake value ratio

D4. Ongoing Studies

Table D4.1. Ongoing Studies

Title / Trial Sponsor	Study Design	Comparators	Patient Population	Primary Outcomes	Estimated Completion Dates
Lecanemab					
A Study to Evaluate Efficacy and Safety of Treatment With Lecanemab in Participants With Preclinical Alzheimer's Disease and Elevated Amyloid and Also in Participants With Early Preclinical Alzheimer's Disease and Intermediate Amyloid (AHEAD 3-45) **Eisai & Biogen** **NCT04468659**	Phase III, QB, RCT	Lecanemab (5 mg/kg + 10 mg/kg biweekly and 5 mg/kg +10 mg/kg monthly,) or PBO for up to 216 weeks.	Inclusion - aged 55 to 80 years - 55 to 64 must have additional risk factors such as first degree relative diagnosed with dementia, possesses at least 1 ApoE ε4 - CDR score of 0 - MMSE score ≥27 - WMS-R LM II >6 Exclusion: - history of ischemic attacks, psychiatric diagnosis or symptoms that could interfere with study procedures - HIV positive	Change in PACC5, change in PET at week 216 weeks	October 25, 2027
A Study to Evaluate Safety, Tolerability, and Efficacy of Lecanemab in Subjects With Early Alzheimer's Disease (Phase II G000-201) **Eisai & Biogen** **NCT01767311**	Phase IIb, MC, DB, PC, OLE	OLE: Off-treatment period (9-59 months, average 24 months) before re-initiating treatment (10 mg/kg biweekly) for 60 months.	Inclusion - AD due to MCI or mild AD dementia - confirmed amyloid positive via PET or CSF - impairment in episodic memory (WMS-IV LMII - MMSE >22 - naïve or stable dose of approved AD medications Exclusion:	OLE: Safety data, MRI assessments of amyloid related to imaging abnormalities, and change from baseline in biomarkers up to 60 months	OLE extension ongoing estimated completion by February 20, 2025. Interim results have been presented.

			- Any medical or neurological condition (other than AD) that might be a contributing cause of the subject's cognitive impairment - Have had a stroke or Transient Ischemic Attack, stroke, or seizures in the past 1 year - Any psychiatric diagnosis or symptoms that could interfere with study procedures - GDS score ≥8 - Contraindications to MRI scanning - Evidence of other clinically significant lesions that could indicate a dementia diagnosis other than AD - Prolonged QT/QTc interval via ECG - Other medical conditions that could prevent patient performing tests accurately		

AD: Alzheimer's disease, ApoE ε4: Apolipoprotein ε4, CDR-GS: Clinical Dementia Rating - Global Score, CDR-SB: Clinical Dementia Rating Scale-Sum of Boxes, CNS: central nervous system, CSF: cerebrospinal fluid, DB: double blind, ECG: electrocardiogram, GDS: Geriatric Depression Scale, LTE: long term extension, MC: multicenter, MMSE: Mini-Mental State Examination, MRI: magnetic resonance imaging, OLE: open-label extension, PC: placebo-controlled, PET: Positron Emission Tomography, RCT: randomized controlled trial, OL: open label, VTE: video teleconference. Source: www.ClinicalTrials.gov.

D5. Previous Systematic Reviews and Technology Assessments

We identified one ongoing health technology assessment (HTA) conducted by NICE and two previously conducted systematic literature reviews (SLR). Both are summarized below.

Additional SLRs were summarized in our previous report on aducanumab and are available in Section D7 of the 2021 review.

NICE

Gantenerumab for Treatment Early Alzheimer's Disease [ID 10668]

As of June 2022, NICE is awaiting development to conduct an appraisal of the clinical and cost-effectiveness of gantenerumab for the treatment of MCI in early AD.

Pang, M. et al. (2022). "Effect of Reduction in Brain Amyloid Levels on Change in Cognitive and Functional Decline in Randomized Clinical Trials: An Instrumental Variable Meta-Analysis"[49]

Investigators reviewed the data of a 2021 variable meta-analysis[109] (cited in our 2021 report on aducanumab) that tested the amyloid hypothesis and resolved data quality issues in an update to ascertain the impact of the reduction in amyloid beta on clinical outcome measures in Alzheimer's disease. In addition to the 14 RCTs from the original publication, Pang et al. included data from the aducanumab-3 PRIME trial and the donanemab TRAILBLAZER-ALZ trial. The authors addressed several consistency issues from the original analysis regarding 12 of the 14 trials related to standard errors and misattributed data points. The included interventions and population characteristics have been summarized previously.[27]

The primary outcome of this analysis was the change in CDR-SB, ADAS-Cog, and MMSE, using the same representation of effect as the original meta-analysis. Sensitivity analyses were performed for 1) all published data, 2) only antibody data, and 3) only published antibody data. In the updated analysis, pooled results for "all data" showed statistically significant evidence of a causal relationship between a reduction in amyloid plaque and a reduction in cognitive and functional decline measured by CDR-SB (0.09; 95% CI: 0.034- 0.15; p=0.0016). This was an improved result over the original meta-analysis, and the sensitivity analyses performed showed similar estimates. There were additional statistically significant causal effects for ADAS-Cog (0.33; 95% CI: 0.12 – 0.55; p=0.0025) and MMSE (0.13; 95% CI, 0.017- 0.24; p=0.024).

While the meta-analysis builds upon Ackley et al. 2021 by including additional trials, there are limitations to this study. Similar to Ackley et al. 2021 meta-analysis, the Pang et al. meta-analysis faced limitations of data availability with many trials not reporting data on change in amyloid and change in a cognitive measure.[51] When data were available, it was predominately aggregated data.

Ackley & Glymour highlight the importance of using individual patient data which would allow the assessment of heterogeneity in response to amyloid reduction and the evaluation of relationship between amyloid reduction and cognition.[51] In addition, Pang et al. assumed no publication bias, non-informative loss to follow-up, consistency across radiotracers, and homogeneity in effects across drugs.[51] Thus, there is a call for pharmaceutical companies to share individual patient data for investigators to more thoroughly examine the relationship between amyloid clearance and slowing of cognitive decline.

Lacorte, E. et al. (2022). "Safety and Efficacy of Monoclonal Antibodies for Alzheimer's Disease: A Systematic Review and Meta-Analysis of Published and Unpublished Clinical Trials"[48]

Investigators identified all available registered trials for monoclonal antibodies (mAbs) evaluating mild cognitive impairment (MCI) due to Alzheimer's Disease (AD) at any stage, on two main registration databases: ClinicalTrials.gov (CT) and the European Clinical Trial Register (EUCT). Studies were excluded if they enrolled healthy participants, investigated drugs other than mAbs, or included any diagnosis other than MCI or AD. Results of the study were summarized narratively, and meta-analyses were conducted on frequency of adverse events (AEs) and severe adverse events (SAEs), frequency of ARIA-E and ARIA-H, mean change in CDR-SB score, and PET standardized uptake value ratio (SUVr). In total, 27 mAbs, assessed through 101 trials, were included in the review. Published and unpublished data were available for 12 of the 27 mAbs.

Based on results from 17 studies on 7 mAbs, there was a significant effect on amyloid burden (as measured by SUVr) for patients treated with mAbs (Standardized mean difference: -0.88; 95% CI -1.30 to -0.47) compared to placebo. Results based on 16 studies on 8 mAbs concluded that patients treated with mAbs had a significantly less cognitive decline on CDR-SB (mean difference: -0.15). However, CDR-SB was mostly considered a secondary outcome, many trials were terminated due to futility, and the difference between groups did not reach clinical significance.

The safety meta-analyses reported a higher frequency of AEs in patients treated with mAbs compared to placebo (Risk Ratio [RR]: 1.04; 95% CI 1.02-1.06). However, no significant difference was shown between groups for SAEs (RR: 1.02; 95% CI 0.96-1.09). Heterogeneity amongst the definitions and reporting of ARIA limited the ability to be able to compare the results across trials. To account for the heterogeneity, the data was stratified by mAb in an additional sensitivity analysis. ARIA-E had an RR of 10.65, with similar results shown in the sensitivity analysis (RR: 10.86). ARIA-H had an overall RR of 1.75, with a higher RR in the sensitivity analysis (RR: 2.11, 95% CI 1.87-2.38). Ten RCTs did not report on ARIA-E or ARIA-H. Donanemab showed the highest risk for ARIA-E (RR: 34.63; 95% CI 4.82-248.76) and ARIA-H (RR: 4.03; 95% CI 2.09-7.79). There were some differences observed between ApoE ε4 carriers (APOE+) and non-carriers (APOE-) for ARIA. Frequency of ARIA-E was slightly higher for carriers (RR: 13.47) than non-carriers (RR: 12.10), and a higher frequency of ARIA-H for non-carriers (RR: 2.18) than carriers (RR: 1.50). When stratified by

mAb, APOE+ participants who received aducanumab had a higher frequency of ARIA-E (RR: 7.83 vs. RR: 2.96), as did APOE+ participant who received donanemab (RR: 30.32 vs. 8.51) or gantenerumab (RR: 41.61 vs. 3.02). ARIA-H frequency was higher for APOE+ participants who received aducanumab (RR: 3.05 vs. 1.85).

Overall, the meta-analysis showed a significant effect of mAbs on amyloid burden, and the CDR-SB results were statistically but not clinically significant. A notable limitation to the analysis was the decision of the trial investigators to only present the clinical outcomes data as means and standard deviations, instead of using response rates or defining number of "responders". Thus, there is currently limited evidence to support that the removal of amyloid can have a substantial impact on cognition. In terms of safety, the meta-analysis concluded that patients have a higher risk of ARIA-E and ARIA-H when treated with mAbs compared to placebo. However, results are limited by the lack of standard definition of ARIA, most likely due to evolution of the definition of ARIA over time, and sensitivity analyses should be interpreted with caution.

Villain, N. et al. (2022). "High-clearance Anti-amyloid Immunotherapies in Alzheimer's Disease. Part 1: Meta-analysis and Review of Efficacy and Safety Data, and Medico-economical Aspects"[50,110]

Investigators reviewed the currently available evidence on the biological and clinical efficacy of high-clearance anti-amyloid immunotherapies in Alzheimer's disease. Using the data available from high-dose aducanumab (ENGAGE and EMERGE), donanemab (TRAILBLAZER-ALZ), high-dose lecanemab (G000-201 and CLARITY AD), and gantenerumab (GRADUATE 1 & 2), the investigators performed a meta-analysis on two cognitive measures (CDR-SB, ADAS-Cog). Data from CLARITY AD and GRADUATE 1 and 2 were only included in the CDR-SB and ARIA-E analyses. MMSE was not available for lecanemab.

The meta-analysis results concluded that there was a significant effect of high clearance amyloid therapies on disease progression for CDR-SB (mean difference: -0.31; 95% CI: -0.50, -0.11; p=0.002), ADAS-Cog (mean difference: -1.25; 95% CI: -1.93, -0.57; p<0.001) but not for MMSE (mean difference: 0.31; 95% CI:-0.19, 0.82; p=0.23). These results were confirmed with fixed effects and Bayesian analyses and when assessed based on disease severity (MCI and mild AD) the improvements were maintained. While the results for CDR-SB support the theory that high-clearance anti-amyloid immunotherapies have a statistically significant effect after 18-27 months, the effect did not reach the established minimal clinically important difference (-1.63, -0.98). To address safety concerns, the investigators also performed a meta-analysis on ARIA. ARIA occurred at a significantly higher rate for participants on high-clearance anti-amyloid therapies, with the highest magnitude of the effect occurring for ARIA-E (RR = 10.98; 95% CI: 7.06- 17.08; p<0.001). Despite in-trial monitoring and management, safety remains a concern.

The investigators maintain that a meta-analysis should not replace the FDA's gold standard for approval, however, the results do confirm the trend regarding high-clearance anti-amyloid therapy's efficacy in removing amyloid. Additionally, the risk/benefit ratio for this class of drugs is still unknown and additional research needs to be done to identify responders. Longer follow-up data is also needed to improve their clinical relevance.

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 & 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	X	X	
	Future related medical costs	X	X	
	Future unrelated medical costs	X	X	
Informal Health Care Sector				
Health-Related Costs	Patient time costs	NA	☐	
	Unpaid caregiver-time costs	NA	X	
	Transportation costs	NA	☐	
Non-Health Care Sector				
Productivity	Labor market earnings lost	NA	X	
	Cost of unpaid lost productivity due to illness	NA	X	
	Cost of uncompensated household production	NA	☐	
Consumption	Future consumption unrelated to health	NA	☐	
Social services	Cost of social services as part of intervention	NA	☐	
Legal/Criminal Justice	Number of crimes related to intervention	NA	☐	
	Cost of crimes related to intervention	NA	☐	
Education	Impact of intervention on educational achievement of population	NA	☐	
Housing	Cost of home improvements, remediation	NA	☐	
Environment	Production of toxic waste pollution by intervention	NA	☐	
Other	Other impacts (if relevant)	NA	☐	

NA: not applicable

Adapted from Sanders et al[111]

Target Population

The model included a hypothetical cohort of individuals with MCI due to AD or mild AD entering the model and receiving either the intervention or comparator treatments. We assumed patients had amyloid positivity confirmed by a reliable method prior to initiating the model. In alignment with the clinical evidence, 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. Individuals 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.

Table E2 details the baseline patient characteristics for the model. Age influenced mortality and quality of life; sex influenced mortality. The baseline clinical stage and setting of care determined which health state and setting of care an individual started the model in.

Table E2. Base-Case Model Cohort Characteristics

	Value	Source	Notes
Mean Age, years	71 years	van Dyck et al., 2022[35]	Weighted average based on sample size of each arm
Female, %	52%		
Clinical Stage, %		Potashman et al., 2020[112]	AD population with underlying amyloid-beta pathology
MCI Due to AD	55%		
Mild AD	45%		
Setting of Care, %		Johnson, 2019[113]	Percent of population ages 65-74 who received long-term services and supports
Community	92%		
Long-Term Care	8%		

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

Treatment Strategies

The list of interventions was developed with input from patient organizations, clinicians, and manufacturers on which treatments to include. Lecanemab was identified as an intervention to be included in the economic evaluation. At the initial stages of this assessment, donanemab was also included as an intervention, but was removed from the assessment following the complete response letter for accelerated approval. Lecanemab was evaluated in addition to supportive care, which could include non-pharmacologic and pharmacologic, but not disease-modifying, interventions. The comparator was supportive care alone.

E2. Model Inputs and Assumptions

Table E3 reports model assumptions along with their rationale that are important to consider when interpreting the findings.

Table E3. Key Model Assumptions

Assumption	Rationale
Lecanemab was effective at slowing the progression of disease while a patient had MCI due to AD or mild AD. Lecanemab was no longer effective once a patient reached moderate AD.	The evidence on clinical outcomes that exists for lecanemab is in early AD. Based on trials of anti-amyloid therapies suggesting no benefit in moderate AD, clinical experts suggested there is likely no effect with anti-amyloid treatments at reducing disease progression once a patient has reached moderate AD. This assumption was tested in scenario analyses.
Individuals stopped receiving lecanemab treatment once they reached moderate AD.	Based on trials of anti-amyloid therapies suggesting no benefit in moderate AD, clinical experts suggested there is likely no effect with anti-amyloid treatments at reducing disease progression once a patient has reached moderate AD, and therefore in our model, treatment stopped once a patient reached moderate AD. In a scenario analysis, we modeled individuals stopping treatment once they reached severe AD. Robust evidence is lacking on lecanemab's effect on clinical outcomes after a patient has stopped the treatment, and thus no additional clinical benefit was assumed after a patient stopped treatment.
All occurrences of ARIA and its associated consequences (on cost, quality of life, and treatment discontinuation) were modeled in the first year of treatment.	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.
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 was collected from a single, primary caregiver.

AD: Alzheimer's disease, ARIA: amyloid-related imaging abnormality, CDR-SB: Clinical Dementia Rating-Sum of Boxes, MCI: mild cognitive impairment

Model Inputs

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, treatment efficacy, the occurrence of adverse events, and discontinuation. Utility estimates were retrieved for both the patient and caregiver. The primary cost inputs included intervention 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.

Clinical Inputs

Transition Probabilities Between Alive Health States

Table E4 provides the annual transition probabilities between each of the alive health states. These estimates were from a recent analysis of AD progression using data from beta-amyloid positive individuals in the National Alzheimer's Coordinating Center database.[114] 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. Transition Probabilities

	MCI Due to AD	Mild AD	Moderate AD	Severe AD	Source
MCI Due to AD	77%	23%	0%	0%	Potashman et al., 2020[114]
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 served as the foundation for transitions to the dead health state, with an increased risk of death associated with AD dependent on the severity of AD. Age- and sex-adjusted mortality was sourced from US-specific life tables. Table E5. provides the relative risk of death from each health state. These relative risks were multiplied by 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[115]	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

Progressions to Long-Term Care

Specific to each health state, the model tracked the setting of care (e.g., community or long-term care). Individuals with AD could progress from community to long-term care; however, once in long-term care, they remained there until death. Table E6. provides the annual probability of progressing to long-term care specific to each alive health state. These estimates are from an analysis that used Consortium to Establish a Registry for Alzheimer's Disease data.[60]

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 the relationship between the relative risk of death for MCI due to AD and mild AD
Mild AD	3.8%	Neumann et al., 1999[60]
Moderate AD	11.0%	
Severe AD	25.9%	

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

Treatment Effectiveness

We assumed that lecanemab influenced disease progression from the MCI due to AD and mild AD health states. The evidence on clinical outcomes that exists for lecanemab is in early AD. Based on trials of anti-amyloid therapies suggesting no benefit in moderate AD, clinical experts suggested there is likely no effect with anti-amyloid treatments at reducing disease progression once a patient has reached moderate AD. We used best available evidence to estimate the effect of lecanemab on slowing disease progression from these health states.

The most relevant clinical evidence for the model includes the rates of transitions among health states defined by AD severity. For lecanemab, Phase III evidence existed on the progression to the next stage of dementia. That evidence served as the best available evidence to estimate the effect of these treatments on slowing disease progression from MCI due to AD and mild AD.

Table E7. presents the estimates of treatment effectiveness we used in the model. These treatment effectiveness estimates were applied to the transition probabilities associated with disease progression reported in Table E4.

Table E7. Treatment Effectiveness* on Slowing Progression

Health State	Lecanemab	Notes
MCI Due to AD	0.69	Equivalent to lecanemab's hazard ratio for slowing the progression of disease
Mild AD	0.69	
Moderate AD	1.00	Patient stopped treatment at moderate AD
Evidence Source	van Dyck et al., 2022[35]	

AD: Alzheimer's disease, CDR-SB: Clinical Dementia Rating-Sum of Boxes, MCI: mild cognitive impairment
*Only applied to health state progressions (i.e., transitions to more severe health states).

Adverse Events

An important adverse event associated with beta-amyloid antibodies is the occurrence of amyloid-related imaging abnormalities (ARIA). ARIA typically occurs early in the treatment course and is often not associated with any symptoms. Table E8. presents the probability of ARIA events for each treatment. We modeled that all ARIA occurred in the first model cycle. Later sections of this Supplement detail how the occurrence of these events influenced cost and quality of life. We did not model a risk of death from an ARIA event, but this is an important area for future research.

Table E8. Adverse Events

Parameter	Lecanemab
Probability of Any ARIA	21.5%
Probability of Symptomatic ARIA	3.5%
Source	van Dyck et al., 2022[35]

ARIA: amyloid-related imaging abnormalities

Discontinuation

Evidence on discontinuation due to adverse events from the pivotal trials was used to estimate discontinuation over the first 12 months on treatment. We assumed individuals discontinued lecanemab due to adverse events halfway through the first model cycle (i.e., six months after starting treatment), in alignment with evidence that most serious adverse events occurred within the first six months of initiating the treatment. No discontinuation due to adverse events was assumed after the first year due to consistent findings that ARIA occurs at the beginning of the treatment course. Table E9. presents the treatment discontinuation rates due to adverse events reported in the pivotal trial.

Table E9. Treatment Discontinuation

Parameter	Lecanemab
AE-related Discontinuation of Treatment	6.9%
Source	van Dyck et al., 2022[35]

AE: adverse event

Separate from discontinuation due to adverse events, treatment stopped once a patient reached moderate AD. Stakeholders suggested there is likely no effect with anti-amyloid treatments at reducing disease progression once a patient has reached moderate AD, and therefore, treatment could discontinue. Discontinuation, either due to adverse event, disease severity or amyloid clearance, occurred halfway through the model cycle.

Utility Inputs

Health state utilities were derived from publicly available literature. These utility estimates primarily came from a cross-sectional study of patients with AD and caregivers with stratifications for both disease severity and setting of care.[116] The utility weights were derived from the Health Utilities Index Mark II (HUI:2) with weights based on the standard-gamble approach.[116] 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.[116] 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.[117] We elected not to select the recent systematic literature review estimates because the utility estimates were not stratified by care setting (e.g., community versus long-term care) and did not report quality-of-life estimates for the caregiver of the patient. Using the utility estimates from the recent systematic review would have required numerous assumptions and additional sources to be able to have utility estimates for individuals that live in the community, individuals that live in long-term care, caregivers of individuals that live in the community, and caregivers of individuals that live in long-term care. We understand the uncertainty

around the utility estimates, and thus we varied each of these inputs across a wide range in sensitivity analyses. As shown in the results from our one-way sensitivity analysis, the range for each of our utility estimates for each level of disease severity includes the point estimate from the recent systematic review.

The model used the utility estimates and the age of the people with AD from the cross-sectional study[116] to calculate a disutility for each disease state and setting of care based off age-adjusted utility estimates. 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. Therefore, the model estimated quality of life was a function of age, disease severity, and setting of care. Table E10. presents the disutilities that were calculated from these estimates. Each disutility was applied for the duration of occupancy in the health state and setting of care.

Table E10. Patient Disutility Estimates

Parameter	Community Setting	Long-Term Care Setting	Source
MCI Due to AD	-0.17	-0.17	Calculated from utility estimates and patient demographics in Neumann et al., 1999[60,116]
Mild AD	-0.22	-0.19	
Moderate AD	-0.36	-0.42	
Severe AD	-0.53	-0.59	

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

In addition to the health state utilities reported in Table E10, a disutility of -0.14 was applied to people with AD experiencing symptomatic ARIA. This disutility was applied for the average duration of ARIA (12 weeks).[92,118] This disutility estimate represents the disutility estimate for headache,[119] which was the most reported symptom among those with symptomatic ARIA.[92,118]

Impacts on the quality of life of caregivers was incorporated in the societal perspective. Caregiver utility estimates were calculated from the same cross-sectional study as the patient utility estimates described above.[116] We used the age of the caregivers in the cross-sectional study[116] to calculate a disutility for each disease state and setting of care. The calculated disutility was directly used in the model. 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.[120] The disutilities that were calculated from these estimates are presented in Table E11. 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	Caregiver Disutility	Source
MCI Due to AD	-0.03	Calculated from utility estimates and patient demographics in Neumann et al., 1999;[60,116] adjusted for AD severity using relationship from Mesterton et al., 2010[120]
Mild AD	-0.05	
Moderate AD	-0.08	
Severe AD	-0.10	

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

Economic Inputs

Drug Utilization

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

- Route of administration
- Dosing
- Frequency of administration
- Duration of treatment

Table E12 reports these characteristics for lecanemab.

Table E12. Treatment Regimen Recommended Dosage

Generic Name	Lecanemab
Manufacturer	Eisai Co., Ltd
Route of Administration	Intravenous
Dosing	10 mg/kg
Frequency of Administration	Every 2 weeks
Duration of Treatment	Until moderate AD
Source	van Dyck et al., 2022[35]

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

Intervention Costs

Given that a net cost is not yet available for lecanemab, we used the wholesale acquisition cost as the price for lecanemab. The annual cost in Table E13 does not include any provider-administered mark-up (assumed to be 6% in addition to the cost in Table E13), or any treatment-associated administration or monitoring costs.

Table E13. Drug Acquisition Costs

Drug	Annual Wholesale Acquisition Cost*	Source
Lecanemab	$26,500	REDBOOK[121]

*Doesn't include any provider-administered mark-up (assumed to be 6% in addition to the cost in table E13).

Non-Intervention Costs

Costs outside of drug acquisition are stratified by perspective below.

Health Care System Costs

Administration Costs

Lecanemab is administered by way of intravenous administration. We assumed an average administration cost of $78.35 per administration (HCPCS code 96365).[122]

Monitoring Costs

For the first year while a patient used lecanemab, we assumed they were monitored for ARIA using brain magnetic resonance imaging (MRI) every three months. Because evidence suggests the vast majority of ARIA occurs within the first year of treatment, no MRIs were modeled after the first year on treatment. We assumed an average brain MRI cost of $261.10 per scan (HCPCS code 70553).[122]

Adverse Event Costs

In addition to the brain MRIs described above for monitoring, if a patient experienced an ARIA event, the patient received a brain MRI every four weeks until the ARIA was either resolved or stabilized.[65] The average duration of an ARIA event was 12 weeks; therefore, a patient that experienced an ARIA event received three additional brain MRIs associated with managing the adverse event. We assumed an average brain MRI cost of $261.10 per scan (HCPCS code 70553).[122]

Non-Treatment Related Health Care Costs

Annual medical costs stratified by disease severity were sourced from a study conducted by Leibson and colleagues.[123] This study reported the average annual inpatient and outpatient medical costs for people who were cognitively normal, had MCI, were newly diagnosed with dementia, and 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 people with AD 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 related and unrelated medical health care utilization, stratified by disease severity. Table E14. reports these cost multipliers that were applied to the health care costs of the general population.

Table E14. Direct Medical Cost Multipliers

Health State	Multiplier	Source
MCI Due to AD	1.12	Leibson et al., 2015[123]
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 lecanemab, we assumed 33.3% of individuals with mild AD received generic donepezil 10 mg once daily ($0.21 per day)[121] and 33.3% of individuals with moderate AD received generic memantine 10 mg twice daily ($0.66 per day).[121,124]

Long-Term Care Costs

For people with AD 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.

Table E15. Long-Term Care Costs

Parameter	Value	Source	Notes
Long-Term Care	$7,394 per month	Administration on Aging[125]	Skilled nursing facility cost

Costs have been inflated from 2016 US dollars to 2021 US dollars using the price index for health care services.[126]

Societal Costs

Patient Productivity Costs

A study published in 2020 by Robinson and colleagues reported that among people with amyloid-beta positive MCI, 20.4% reported still working, with 4.9% of those who worked reporting a reduction in work due to AD.[127] Similarly, among people 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.[127] We assumed 0% of individuals with moderate and severe AD work with the reason for non-employment not attributed to AD. The average age of the population in the Robinson study was comparable to the average age of our modeled cohort. For those individuals who reduced work due to AD, we assigned lost productivity costs of 20 hours per week. The average hourly wage of $32.46 was used to monetize the lost productivity.[128]

Caregiver Productivity Costs

The Robinson et al., 2020 study also reported caregiver time spent caregiving for individuals with MCI.[127] A separate source by Haro and colleagues reported caregiver time spent caregiving for community-dwelling people with mild, moderate, and severe AD.[129] Table E16. reports the average caregiver time spent caregiving for community-dwelling people with AD in each health state that were used in the model for people with AD dwelling in the community. Time includes time spent providing supervision and activities of daily living (basic and instrumental).

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

Health State	Value	Source
MCI Due to AD	69 hours/month	Robinson et al., 2020[127]
Mild AD	113 hours/month	Haro et al., 2014[129]
Moderate AD	169 hours/month	
Severe AD	298 hours/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 people with AD was 44% that of caregiver time spent with community-dwelling people with AD; and thus the estimates reported were multiplied by 44% to estimate the caregiver time spent for long-term-care-dwelling people with AD.[130] The average hourly wage of $32.46 was used to monetize the time spent caregiving.[128]

Caregiver Direct Medical Costs

Table E17. presents the direct medical costs for the primary caregiver of a patient with AD. These are the same values we used in our prior AD review but have been inflated to 2021 US dollars.

Table E17. Caregiver Direct Medical Costs

Health State	Value	Source
MCI Due to AD	$460 per month	Robinson et al, 2020[127]
Mild AD	$965 per month	
Moderate AD	$1,544 per month	Robinson et al, 2020[127] & Mesterton et al., 2010[120]
Severe AD	$1,930 per month	

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

E3. Results

Description of evLY Calculations

The evLY 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 evLY.

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. [131]

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. We use the same calculations in the comparator arm to derive its evLY.

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

E4. Sensitivity Analyses

Table E18. Credible Intervals from Probabilistic Sensitivity Analysis for Lecanemab versus Supportive Care

Model Outcome	Lecanemab	Supportive Care
Total Costs	$492,000	$364,000
Total QALYs	3.87 (3.42, 4.40)	3.35 (3.08, 3.61)
ICER ($/QALY)	$248,000	
Total evLYs	3.99 (3.47, 4.57)	3.35 (3.08, 3.61)
ICER ($/evLY)	$200,000	

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

E5. Scenario Analyses

We conducted numerous scenario analyses to test the structural assumptions that were made.

Scenario Analysis 1: Treatment Stop at Severe AD

The incremental cost-effectiveness ratios are provided in the main report, but we include the model outcomes in Table E19. and Table E20.

Table E19. Model Outcomes for the Health Care Sector Perspective, Treatment Stop at Severe AD

Treatment	Intervention Cost*	Total Cost	Life Years	QALYs	evLYs	Years in the Community
Lecanemab	$137,000	$529,000	6.34	3.93	4.08	4.28
Supportive Care	$0	$363,000	5.77	3.34	3.34	3.69

evLYs: equal-value life years, QALYs: quality-adjusted life years

*Intervention cost doesn't include provider administered mark-up (modeled as 6%), monitoring costs, or administration costs.

Table E20. Model Outcomes for the Modified Societal Perspective, Treatment Stop at Severe AD

Treatment	Intervention Cost*	Total Cost	Life Years	QALYs	evLYs	Years in the Community
Lecanemab	$137,000	$833,000	6.34	3.57	3.76	4.28
Supportive Care	$0	$670,000	5.77	2.98	2.98	3.69

evLYs: equal-value life years, QALYs: quality-adjusted life years

*Intervention cost doesn't include provider administered mark-up (modeled as 6%), monitoring costs, or administration costs.

Scenario Analysis 2: Updated Caregiver Disutility Estimates

In this scenario analysis, we updated the source for the caregiver disutility estimates to estimates reported in a recent conference poster.[132] Table E21 reports the caregiver disutilities, stratified by patient health state and setting of care, that were applied in this scenario analysis. These disutilities were not used in our base-case analysis for multiple reasons including the general appropriateness of using time tradeoff for eliciting utilities for a caregiver, the challenge for a person from the general population to detangle the patient health states from the caregiver quality of life in this exercise, the uncertainty in how the domains in the study mapped to our health states and setting of care, the limited information available regarding the framing of the questions, and the small sample size.

Table E21. Caregiver Disutilities for Scenario Analysis

Health State	Community Setting	Long-term Care Setting
MCI due to AD	-0.04	-0.04
Mild AD	-0.06	-0.11
Moderate AD	-0.20	-0.14
Severe AD	-0.36	-0.21

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

These disutilities are larger than the estimates used in our base-case, and thus generated lower incremental cost-effectiveness ratios from the societal perspective. Table E22. reports the updated societal perspective cost-effectiveness estimates assuming these disutilities.

Table E22. Incremental Cost-Effectiveness Ratios, Updated Caregiver Disutility Estimates

Lecanemab vs. Supportive Care			
Perspective	**Cost per Life Year Gained**	**Cost per QALY Gained**	**Cost per evLY Gained**
Societal	$265,000	$213,000	$163,000

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

E6. Model Validation

Model validation followed standard practices in the field. We used several approaches to validate the model. First, we provided the 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 varied model input parameters to evaluate face validity of changes in results. We performed model verification for model calculations using internal reviewers. As part of ICER's efforts in acknowledging modeling transparency, we also shared the model with the relevant manufacturers for external verification shortly after publishing the draft Evidence Report. Finally, we compared results to other cost-effectiveness models in this clinical area.

Prior Economic Models

We compared our findings for lecanemab to a peer-reviewed publication on the potential economic value of lecanemab.[133] The peer-reviewed publication used a patient level simulation model (AD ACE) with the assumption that the treatment effect was driven by reductions in amyloid PET levels using evidence from the Phase II trial.[133] In our model, we used a Markov model with the treatment effect modeled as the hazard ratio for observed progressions to the next stage of dementia using evidence from the Phase III trial. Despite the difference in structure (Markov model versus patient level simulation) and treatment effectiveness estimates (hazard ratio on progressions to next stage of dementia versus amyloid PET level), our findings are relatively similar. The peer-reviewed publication reported a threshold range (from $50,000 to $200,000 per QALY gained) of $9,000 to $38,000.[133] Our reported threshold range (from $50,000 to $200,000) was $3,000 to $29,000.

Differences in the findings can largely be explained by the fact that our model used direct clinical outcome data from the Phase III trial whereas the peer-reviewed publication used amyloid PET level as a surrogate predictor of clinical outcomes.

There is also a peer-reviewed publication on the cost-effectiveness of a hypothetical disease-modifying treatment for AD that modeled various treatment strategies, including a continuous dosing strategy and a fixed duration strategy.[134] The peer-reviewed publication used model inputs for a hypothetical intervention and reported an incremental cost-effectiveness ratio of $612,000 per QALY gained under a continuous treatment strategy and an incremental cost-effectiveness ratio of $126,000 per QALY gained under a fixed duration strategy where 40% discontinued at 6 months and 100% discontinued at 18 months.[134] Our model nearly replicated those incremental cost-effectiveness ratios when we made similar model assumptions (e.g., treatment effect, treatment duration, discontinuation, treatment cost). When we updated our model to reflect the inputs used for the hypothetical treatment that was modeled in this peer-reviewed publication, our model generated an incremental cost-effectiveness ratio of $625,000 per QALY gained under a continuous treatment strategy and an incremental cost-effectiveness ratio of $143,000 per QALY gained under a fixed duration strategy.

In our prior AD review that included aducanumab, we calculated an optimistic treatment benefit scenario that closely reflects the assumptions we have made in our base-case analysis of this review.[8] In the optimistic treatment benefit scenario of our prior AD review, we assumed the hazard ratio for the trial that showed a benefit (i.e., we did not blend the hazard ratio with the trial that did not show a benefit) and we assumed the same treatment effect for transitions out of MCI and mild. The threshold range, using thresholds of $100,000 to $150,000, for aducanumab based on the optimistic treatment benefit scenarios was $11,000 to $25,000. This is similar to the threshold range we report for lecanemab. The threshold range, using thresholds of $100,000 to $150,000, for lecanemab was $8,900 to $21,500. This is slightly lower than the range for aducanumab that assumed the optimistic treatment benefit due to lower discontinuation for lecanemab (which increases treatment costs for the cohort), a higher baseline starting age for lecanemab, and differences in how discontinuation was programmed.