Medical Policy

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Title: Monoclonal Antibodies for Treatment of Alzheimer Disease

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Populations	Interventions	Comparators	Outcomes
Individuals: • With early Alzheimer disease (mild cognitive impairment or mild dementia due to Alzheimer disease)	Interventions of interest are: • Lecanemab	Comparators of interest are: • Standard of care	Relevant outcomes include: • Disease-specific survival • Change in disease status • Functional Outcomes • Health status measures • Quality of life • Treatment-related mortality • Treatment-related morbidity

DESCRIPTION

Alzheimer disease (AD) is a neurodegenerative disorder leading to progressive, irreversible destruction of neurons and loss of cognitive function and memory. Over time, individuals with AD

progress to severe dementia, loss of independence, and death. Extracellular deposits of amyloid beta, referred to as amyloid plaques, are considered a hallmark of the disease. Beta-amyloid monomers lead to formation of beta oligomers and fibrils, are deposited as plaques, and then interact with tau fibrils, leading to formation of neuro-fibrillatory tangles. These pathophysiological changes and clinical manifestations of AD are progressive and occur along a continuum, and accumulation of amyloid beta may begin 20 years or more before symptoms arise. Monoclonal antibodies that reduce amyloid beta plaques have been approved by the U.S. Food and Drug Administration.

OBJECTIVE

The objective of this evidence review is to assess whether treatment with monoclonal antibodies improves the net health outcome in individuals with early Alzheimer disease (mild cognitive impairment or mild dementia due to Alzheimer disease).

BACKGROUND

Alzheimer Disease

Alzheimer disease (AD) is a fatal neurodegenerative disease that causes progressive loss in memory, language, and thinking, with the eventual loss of ability to perform social and functional activities in daily life. Survival after a diagnosis of dementia due to AD generally ranges between 4 and 8 years; however, life expectancy can be influenced by other factors, such as comorbid medical conditions. It is estimated that 6.2 million Americans aged 65 and older are currently living with AD dementia, and the number is projected to reach over 12 million by 2050.[1,]

Pathophysiology

The pathologic hallmarks of AD are extracellular deposits of amyloid beta, referred to as amyloid plaques, and intracellular aggregates of hyperphosphorylated tau in the form of neurofibrillary tangles. 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. Generally referred to as the "amyloid hypothesis", it is believed that aggregation of amyloid beta oligomers in the brain leads to amyloid plaques and it is thought to be the primary driver of the disease process. Amyloid aggregation is thought to precede accumulation of tau pathology and neurodegeneration. These changes in the brain result in widespread neurodegeneration and cell death, and ultimately cause the clinical signs and symptoms of dementia.[2,3,]

Salient known risk factors for AD are older age, genetics, and family history. Of these, increasing age has the largest known impact on risk of developing AD. While several genes have been found to increase the risk of AD, the ε4 allele of the apolipoprotein E (*ApoE*) gene is the strongest known genetic risk factor.[4,5,] Having a single copy of the gene is associated with a 2- to 3-fold increase in developing AD while 2 copies of the gene may increase risk of AD by as much as 15 times.[6,] Approximately two-thirds of pathology-confirmed AD cases are ε4 positive (homozygous or heterozygous), compared with about 15% to 20% of the general population.[5,] Autosomal dominant genetic mutations are estimated to account for less than 1% of AD cases.[7,]

The pathophysiological changes and clinical manifestations of AD are progressive and occur along a continuum, and accumulation of amyloid beta may begin 20 years or more before symptoms arise.[8,] The National Institute on Aging-Alzheimer's Association (NIA-AA) have created a "numeric clinical staging scheme" (Table 1) that avoids traditional syndromal labels and is applicable for only those in the Alzheimer continuum. This staging scheme reflects the sequential evolution of AD from an initial stage characterized by the appearance of abnormal AD biomarkers in asymptomatic individuals. As biomarker abnormalities progress, the earliest subtle symptoms become detectable. Further progression of biomarker abnormalities is accompanied by progressive worsening of cognitive symptoms, culminating in dementia. This numeric cognitive staging scheme is not designed to be used in a clinical setting but to be used for interventional trials. The phase 3 randomized controlled trials (RCTs) for aducanumab were stratified to include 80% of stage 3 patients and 20% of stage 4 patients. This numeric staging scheme is very similar to the categorical system for staging AD outlined in the Food and Drug Administration (FDA) guidance for industry pertaining to developing drugs for treatment of early AD.[9,]

Clinical criteria for diagnosing AD are informed by the NIA-AA 2011 guidelines.[10,11,] Mild cognitive impairment (MCI) lies between the cognitive changes of normal aging and dementia. Mild cognitive impairment is a syndrome in which persons experience memory loss (amnestic MCI) or loss of thinking skills other than memory loss (non-amnestic MCI), to a greater extent than expected for age, but without impairment of day-to-day functioning.[10,] Individuals with MCI are at increased risk of developing dementia (whether from AD or another etiology), but many do not progress to dementia, and some get better. Dementia is a syndrome involving cognitive and behavioral impairment in an otherwise alert patient, due to a number of neurological diseases, alone or combined. It is not a specific cause or disease process itself. The impairment must involve a minimum of 2 domains (memory, reasoning, visuospatial abilities, language or personality behaviors), impact daily functioning, represent a decline from previous levels of functioning, not be explainable by delirium (a temporary state of mental confusion and fluctuating consciousness from various causes) or a major psychiatric disorder, and be objectively documented by a "bedside" mental status exam (e.g., the mini-mental status exam) or neuropsychological testing.[11,] These guidelines describe core clinical criteria for "all-cause" dementia and "probable AD" dementia. Briefly, "probable AD" dementia must first meet the criteria for "all-cause" dementia. Additionally, there must be: (a) insidious onset; (b) documented worsening of cognition; (c) exclusion of major concomitant cerebrovascular disease (as most individuals with AD have some level of this as well); and (d) exclusion of alternative diagnoses (e.g., dementia with Lewy bodies, behavioral variant frontotemporal dementia, progressive aphasia, or other neurological disease associated with dementia). A clinical diagnosis of "possible AD" dementia would meet the criteria for "probable AD" with the exception of having an "atypical course" (e.g., sudden rather than insidious onset) or an "etiologically mixed presentation."

Many tests are available in the market to detect the underlying core pathology such as certain biomarkers in the cerebrospinal fluid (CSF) (e.g., decreased amyloid beta and increased CSF tau protein levels) and on imaging (e.g., amyloid on positron emission tomography [PET] scans). Approved amyloid PET tracers in the US include [^{18}F]-florbetapir, [^{18}F]-flutemetamol, and [^{18}F]-florbetaben. In addition, there are several blood-based tests for amyloid beta confirmation that are currently in development in the US. Cerebrospinal fluid tests and amyloid PET tracers are routinely used in the enrollment of participants in contemporary AD studies.[12,]

Current Treatment

Treatment goals for patients with AD are often directed to maintain quality of life, treat cognitive symptoms, and manage behavioral and psychological symptoms of dementia. Treatment remains largely supportive, including creation and implementation of individualized dementia care plans, caregiver education and support, care navigation, care coordination, and referral to community-based organizations for services (e.g., adult day care, caregiver training).[13,] Non-pharmacologic treatments include physical activity[14,15,] as well as behavioral strategies to ameliorate neuropsychiatric symptoms (e.g., agitation, delusions, disinhibition), and problem behaviors (e.g., resistance to care, hoarding, obsessive-compulsive behaviors).[16,] Currently, FDA-approved drugs for AD include cholinesterase inhibitors, donepezil, rivastigmine, and galantamine, and the N-methyl-D-aspartate antagonist, memantine. 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, focus on managing cognitive and functional symptoms of the disease and have not been shown to alter disease trajectory. The evidence for efficacy is limited and these agents are associated with significant side effects.[16,17,]

Table 1. National Institute on Aging-Alzheimer's Association Numerical Clinical Staging for Individuals in the Alzheimer Continuum[a]

Stage	Stage 1	Stage 2	Stage 3	Stage 4	Stage 5	Stage 6
Severity	**Pre-clinical**	**Pre-clinical**	**MCI due to Alzheimer disease**	**Mild Dementia**	**Moderate Dementia**	**Severe Dementia**
Clinical Features	• Performance within expected range on objective cognitive tests. • No evidence of recent cognitive decline or new neurobehavioral symptoms.	• Normal performance within expected range on objective cognitive tests. • Transitional cognitive decline (change from individual baseline within past 1 to 3 years, and persistent for at least 6 months). • Mild neurobehavioral changes may coexist or	• Performance in the impaired/abnormal range on objective cognitive tests. • Evidence of decline from baseline. • Performs daily life activities independently, but cognitive difficulty may result in detectable but mild functional impact on the more complex activities of daily life.	• Substantial progressive cognitive impairment affecting several domains, and/or neurobehavioral disturbance. • Clearly evident functional impact on daily life, affecting mainly instrumental activities. • No longer fully independent/requires occasional assistance with daily life activities.	• Progressive cognitive impairment or neurobehavioral changes. • Extensive functional impact on daily life with impairment in basic activities. • No longer independent and requires frequent assistance with daily life activities.	• Progressive cognitive impairment or neurobehavioral changes. • Clinical interview may not be possible. • Complete dependency due to severe functional impact on daily life with impairment in basic activities, including basic self-care.

Stage	Stage 1	Stage 2	Stage 3	Stage 4	Stage 5	Stage 6
		may be the primary complaint rather than cognitive. • No functional impact on daily life activities.				

Adapted from Table 6, Jack et al (2018)[18,]
CSF: cerebrospinal fluid; FDG: fluorodeoxyglucose; MCI: mild cognitive impairment; MRI: magnetic resonance imaging; PET: positron emission tomography.
[a]Applicable only to individuals in the Alzheimer continuum that fall into 1 of the 4 biomarker groups: 1) A+T+N+ 2) A+T-N- 3) A+T+N- 4) A+T-N+ where A: Aggregated amyloid beta or associated pathologic state (CSF amyloid beta$_{42}$, or amyloid beta$_{42}$/amyloid beta$_{40}$ ratio or Amyloid PET), T: Aggregated tau (neurofibrillary tangles) or associated pathologic state (CSF phosphorylated tau or Tau PET) and N: Neurodegeneration or neuronal injury (anatomic MRI, FDG PET or CSF total tau)
For stages 1 to 6: Cognitive test performance may be compared to normative data of the investigator's choice, with or without adjustment (choice of the investigators) for age, sex, education, etc.
For stages 2 to 6: Although cognition is the core feature, neurobehavioral changes—for example, changes in mood, anxiety, or motivation—may coexist.
For stages 3 to 6: Cognitive impairment may be characterized by presentations that are not primarily amnestic.

REGULATORY STATUS

Aducanumab

In June 2021, aducanumab (Aduhelm; Biogen) was approved by the FDA for treatment of AD. This indication was approved under accelerated approval based on the reduction in amyloid beta plaques observed in patients treated with aducanumab. In January 2024, Biogen announced that the company was discontinuing the development and commercialization of Aduhelm.[19,]

Lecanemab

In January 2023, lecanemab (Leqembi; Eisai) was approved by the FDA for treatment of AD. This indication was approved under accelerated approval based on the reduction in amyloid beta plaques observed in patients treated with lecanemab.

The FDA, under the accelerated approval regulations (21 CFR 601.41), required that Eisai conduct a RCT to evaluate the efficacy of lecanemab compared to an appropriate control for the treatment of AD. The trial was to be of sufficient duration to observe changes on an acceptable endpoint in the patient population enrolled in the trial. The trial fulfilling this requirement was the Phase 3 Study 301 (CLARITY AD) trial that was completed and reported in the final report of the Biologics License Application (BLA) submission to the FDA.

The FDA convened a meeting of the Peripheral and Central Nervous System (PCNS) Drugs Advisory Committee Meeting on June 9, 2023 to discuss the BLA submission. The Committee

members voted unanimously (6 to 0) that the results of Study 301 (CLARITY AD) verified the clinical benefit of lecanemab for the treatment of AD.

On July 6, 2023, the FDA converted the accelerated approval of Leqembi to traditional approval for the treatment of AD in patients with MCI or mild dementia stage of disease. The label includes a boxed warning for amyloid related imaging abnormalities (ARIA), in general, and emphasizing that ApoE ε4 homozygotes have a higher incidence of ARIA.

Eisai submitted a supplement to the Leqembi BLA in April 2024 to support monthly intravenous (IV) instead of biweekly IV dosing during maintenance therapy.

Eisai began a rolling submission of a BLA for the subcutaneous formulation of Leqembi in May 2024.

Donanemab
On July 2, 2024 Donanemab (Kisunla™) received traditional approval by the FDA for the treatment of early AD. Treatment with Donanemab (Kisunla™) should be initiated in patients with mild cognitive impairment or mild dementia due to Alzheimer's disease who have confirmation of elevated beta-amyloid in the brain. The label includes a boxed warning for amyloid related imaging abnormalities (ARIA), in general, and emphasizing that ApoE ε4 homozygotes have a higher incidence of ARIA.

POLICY

A. Lecanemab may be considered **medically necessary** for individuals if they meet **ALL** of the following criteria:
   1. **Initiation of therapy:**
      a. Meets criteria for mild cognitive impairment (MCI) or mild dementia stage of Alzheimer disease (AD) (see Policy Guidelines);
      b. Presence of amyloid beta pathology (see Policy Guidelines);
      c. Access to an appropriate healthcare delivery model (see Policy Guidelines);
      d. No contraindication(s) to MRI scanning;
      e. MRI scan completed within previous 12 months which does not show:
         i. Evidence of a non-AD dementia;
         ii. Evidence of significant pathological findings on brain MRI (see Policy Guidelines);
      f. Does not have:
         i. Concurrent neurological condition(s), other than MCI or AD, contributing to cognitive impairment
         ii. History of stroke, transient ischemic attacks or seizures within 12 months prior to initiating treatment with lecanemab;
         iii. Bleeding disorder that is not under adequate control (including a platelet count <50,000 or international normalized ratio [INR] >1.5);
      g. If the individual is receiving anticoagulant therapy, anticoagulant status should be optimized and individual should be on a stable dose for 4 weeks prior to initiating treatment with lecanemab;
      h. Not receiving another anti-amyloid monoclonal antibody (e.g., aducanumab).
      i. Is prescribed in accordance with the U.S. Food and Drug Administration (FDA) approved prescribing label (see Policy Guidelines).

B. Incremental reauthorization for lecanemab may be considered **medically necessary** for individuals if they meet all the following criteria:
   1. **Continuation of therapy:**
      a. Has not progressed to moderate or severe dementia;
      b. Has received MRI during treatment with lecanemab according to schedule recommended in FDA label to monitor for amyloid-related imagining abnormalities (ARIA) (see Policy Guidelines) which does not show:
         i. ARIA of the severity that meets recommendations for dosing interruptions provided in FDA label (see Policy Guidelines);
         ii. Evidence of significant pathological findings on brain MRI (see Policy Guidelines);
         iii. Evidence of stroke.

C. Lecanemab is considered **experimental / investigational** when the above criteria are not met.

D. The use of all other monoclonal antibodies is considered **experimental / investigational** for all indications, including treatment of Alzheimer's Disease (AD).

POLICY GUIDELINES

A. **Aducanumab**

In January 2024, Biogen announced that the company was discontinuing the development and commercialization of Aduhelm® (aducanumab). Biogen stated that individuals receiving Aduhelm in clinical trials will continue to have it available until May 1, 2024, and individuals receiving it by prescription will have it available until Nov. 1, 2024.

B. **Lecanemab**

1. **Recommended Dose**

Per the label, the recommended dosage is 10 mg/kg that must be diluted then administered as an intravenous infusion over approximately 1 hour, once every 2 weeks.

2. **Monitoring**

The product label of lecanemab recommends that a baseline brain MRI within 1 year must be done prior to initiating treatment due to the risk of ARIA. Subsequently, MRI should be repeated prior to the fifth, seventh, and fourteenth infusions. Follow recommendations for dosing interruptions in individuals with ARIA as specified in the US FDA-approved prescribing label.

3. **Boxed Warning**

The product label includes a boxed warning regarding the risk of ARIA. The warning states that providers should discuss the potential risk of serious adverse events associated with ARIA when deciding to initiate treatment. The warning also states that individuals who are ApoE ε4 homozygotes have a higher incidence of ARIA and testing for ApoE ε4 status **should be performed** prior to initiation of treatment to inform the risk of developing ARIA.

4. **Healthcare Delivery Model**

An appropriate healthcare delivery model for lecanemab would include care delivered in a setting that may include access to:

a. Trained and experienced psychometricians, neuropsychiatrists, neurologists, geriatric psychiatrists and/or geriatricians to diagnose and stage Alzheimer disease (AD);
b. Trained and experienced radiologists for MRI interpretation for ARIA-E, ARIA-H, superficial siderosis and micro hemorrhages;
c. Protocol for the management of serious and severe ARIA;
d. Individuals receiving lecanemab preferably has an informant/care partner as part of discussion for treatment initiation, continuation and monitoring.

5. **Diagnosis of Mild Cognitive Impairment or Mild Dementia**

Lecanemab was evaluated in the pivotal trial called Clarity AD (ClinicalTrials.gov number, NCT03887455). The Clarity AD trial criteria for diagnosis of mild cognitive impairment or mild dementia were as follows:

Mild cognitive impairment (MCI) due to AD–intermediate likelihood:

a. Meet the National Institute of Aging–Alzheimer's Association (NIA-AA) core clinical criteria for MCI due to AD–intermediate likelihood;

b. Have a global Clinical Dementia Rating (CDR) score of 0.5 and a CDR Memory Box score of 0.5 or greater;
c. Report a history of subjective memory decline with gradual onset and slow progression over the last 1 year which is corroborated by an informant.

Mild AD dementia:
a. Meet the NIA-AA core clinical criteria for probable AD dementia;
b. Have a global CDR score of 0.5 to 1.0 and a CDR Memory Box score of 0.5 or greater.

Other Clarity-AD criteria related to cognitive impairment:
a. Mini Mental State Examination (MMSE)* score ≥ 22;
b. 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)

*Given that the MMSE is copyrighted and is not free to use, responses from clinical input and the criteria from the Veterans Affairs (VA) indicate that the Short Test of Mental Status (STMS > 24), Montreal Cognitive Assessment (MoCA > 15), or Saint Louis University Mental Status (SLUMS) > 16 may be reasonable alternatives when MMSE is not available.

6. **Positive amyloid pathology**
The Clarity AD trial criteria for positive biomarker for brain amyloid pathology includes at least 1 of the following:
a. Positron emission tomography (PET) assessment of imaging agent uptake into brain within 12 months;
b. Cerebrospinal fluid (CSF) assessment of t-tau/Aβ[1-42].

7. **Exclusionary pathological findings on MRI**
The Clarity AD trial criteria excluded individuals with significant pathological findings on brain MRI, including but not limited to:
a. more than 4 microhemorrhages (defined as 10 mm or less at the greatest diameter);
b. a single macrohemorrhage greater than 10 mm at greatest diameter;
c. an area of superficial siderosis;
d. evidence of vasogenic edema;
e. evidence of cerebral contusion, encephalomalacia, aneurysms, vascular malformations, or infective lesions;
f. evidence of multiple lacunar infarcts or stroke involving a major vascular territory, severe small vessel, or white matter disease;
g. space occupying lesions;
h. brain tumors (however, lesions diagnosed as meningiomas or arachnoid cysts and less than 1 cm at their greatest diameter need not be exclusionary).

Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

RATIONALE

This evidence review was created with searches of the PubMed database. The most recent literature update was performed through May 03, 2024.

Evidence reviews assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are length of life, quality of life, and ability to function including benefits and harms. Every clinical condition has specific outcomes that are important to patients and to managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of a technology, 2 domains are examined: the relevance and the quality and credibility. To be relevant, studies must represent 1 or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. Randomized controlled trials are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

Promotion of greater diversity and inclusion in clinical research of historically marginalized groups (e.g., People of Color [African-American, Asian, Black, Latino and Native American]; LGBTQIA (Lesbian, Gay, Bisexual, Transgender, Queer, Intersex, Asexual); Women; and People with Disabilities [Physical and Invisible]) allows policy populations to be more reflective of and findings more applicable to our diverse members. While we also strive to use inclusive language related to these groups in our policies, use of gender-specific nouns (e.g., women, men, sisters, etc.) will continue when reflective of language used in publications describing study populations.

EARLY ALZHEIMER DISEASE

Clinical Context and Therapy Purpose

The purpose of monoclonal antibodies such as lecanemab is to provide a treatment option that is an alternative to or an improvement on existing therapies for individuals with early Alzheimer disease (AD; mild cognitive impairment [MCI] or mild dementia due to AD).

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is individuals with early AD.

Interventions

The therapy being considered is monoclonal antibodies (MABs) with U.S. Food and Drug Administration (FDA) approval, which includes aducanumab and lecanemab. The accumulation of amyloid beta plaques in the brain is a defining pathophysiological feature of AD. Both

aducanumab-avwa and lecanemab-irmb are immunoglobulin gamma 1 (IgG1) monoclonal antibodies directed against aggregated soluble and insoluble forms of amyloid beta.

In January 2024, Biogen announced that they were discontinuing the development and commercialization of aducanumab.

Comparators

The following practice is currently being used to treat early AD. Currently approved AD treatments include the cholinesterase inhibitors, donepezil, rivastigmine, and galantamine, and the N-methyl-D-aspartate antagonist, memantine. None of these agents addresses the underlying pathology of the disease. Their effects are reversible and lessen over time due to the continued progression of the disease process.

Outcomes

The general outcomes of interest are disease-specific survival, change in disease status, functional outcomes, health status measures, quality of life, and treatment-related mortality and morbidity. Follow-up at 2 to 5 years is of interest to monitor outcomes. See Table 2 for the description and relevance of specific outcome measures considered in this review.

As per the FDA 2018 draft guidance for developing drugs for treatment of early AD, treatment for mild to moderate AD dementia (corresponding to stages 4 and 5) would be considered substantially effective if there is improvement on a core symptom (e.g., a measure of cognition) and a global clinical measure (e.g., a clinician's judgement of change) or a functional measure (e.g., activities of daily living).[9,] For studies including prodromal individuals with MCI (corresponding to Stage 3 in the FDA 2018 draft guidance), the FDA requires only a statistically significant change on a prespecified composite measure that includes cognition and daily function combined, as a demonstration of substantial effectiveness. In the 2013 draft guidance, the agency specifically recommended the Clinical Dementia Rating Sum of Boxes (CDR-SB) as a composite measure that had shown validity and reliability for this purpose. No quantified minimum differences were specified, but the rationale was that such a composite measure serves as an indicator of change in both the core or cognitive outcome.[19,] Meeting minimal clinically important difference (MCID) thresholds, however, are not requisites for the FDA to conclude a trial shows substantial effectiveness or to authorize marketing approval.[20,]

Table 2. Health Outcome Measures That May Be Relevant to Early Alzheimer Disease

Outcome Measure	Description	Scale	Clinically meaningful difference/Comment
Clinical Dementia Rating-Sum of Boxes (CDR-SB)	• Commonly used in AD clinical drug trials but not in routine clinical setting • Rating is obtained through a semi-structured interview of the patient and a reliable informant or collateral source (e.g., family member) • Scoring requires extensive training and is subject to	• Prespecified severity anchors range from none = 0, questionable = 0.5, mild = 1, moderate = 2 to severe = 3 (the personal care domain omits the 0.5 score)	• Shown to be sufficiently sensitive and specific to detect change over time in early symptomatic AD participants[21,] • Average increase in 1 to

Outcome Measure	Description	Scale	Clinically meaningful difference/Comment
	variability among ethnicity and languages • Cost/licensing requirements for usage • There are a total of 6 domains (first 3 for cognition and last 3 for functioning) 1. 1. Memory 2. Orientation 3. Judgment/problem-solving 4. Community affairs 5. Home/hobbies 6. Personal care	• The "sum of boxes" scoring methodology sums the score for each of the 6 domains and provides a value ranging from 0 to 18 that can change in increments of 0.5 or greater • Higher scores indicate greater disease severity	2 points is indicative of a clinically meaningful decline[22,] • For MCI and mild AD, differences of 0.98 and 1.63 points represent clinically meaningful change[20,]
Mini-Mental State Examination (MMSE)	• Widely used performance-based test of global cognitive status • Consists of 11 tasks assessing orientation, word recall, attention and calculation, language abilities, and visuospatial functions[23,] • Takes 5 to 8 minutes to administer • Designed to be administered in a doctor's office or clinical setting but can also be taken in the home. Scoring is straight-forward, and family members or loved ones can manage the administration and scoring process without special training • Administered to patient	• Scores from the 11 tests are combined to obtain the total score, which ranges from 0 to 30 • Lower scores over time indicate increasing cognitive impairment	• Average decrease in 1 to 3 points is indicative of a clinically meaningful decline[22,] • For MCI and mild AD, differences of 1.26 and 2.32 points represent clinically meaningful change[20,] • Limitations include lack of sensitivity to change, particularly in earlier disease stages, substantial ceiling effects, sensitivity to practice effects, scores are impacted by patients' educational achievement, and learning effects are

Outcome Measure	Description	Scale	Clinically meaningful difference/Comment
			observed[24,25,26,27,] • The test also lacks items reflecting executive dysfunctions often seen in early clinical stages
Alzheimer's Disease Assessment Scale – Cognitive 13-Item Scale (ADAS-Cog 13)	• Comprises both cognitive tasks and clinical ratings of cognitive performance[28,29,] • Scale captures word recall, ability to follow commands, the ability to correctly copy or draw an image, naming, the ability to interact with everyday objects, orientation, word recognition, memory, comprehension of spoken language, word-finding, and language ability, with a measure for delayed word recall and concentration/distractibility • Conducted by an interviewer/rater (ie, trained health care professional) • Administered to patient	• Scores range from 0 to 85 • Higher scores indicated greater severity	• MCID in mild AD is 3 points[30,] • Low sensitivity to detect a change in MCI due to AD[31,32,]
Alzheimer's Disease Cooperative Study – Activities of Daily Living – Mild Cognitive Impairment (ADCS-ADL-MCI)	• Reflects caregiver observations about the patient's actual functioning over the previous month and assesses the change in the functional state of the participant over time • Conducted by an interviewer/rater (ie, trained health care professional) • Administered to caregivers	• Consists of 17 instrumental items (e.g., shopping, preparing meals, using household appliances) and 1 basic item (getting dressed) • Total score ranges from 0 to 53 • Lower scores indicate greater	• Literature search did not yield citations supporting MCID values • The ADCS-ADL has been used as an endpoint in AD clinical trials[33,34,35,]

Outcome Measure	Description	Scale	Clinically meaningful difference/Comment
		severity/functional deterioration	
Neuropsychiatric Inventory-10 (NPI-10)	• Systematically indexes the presence, frequency, and severity of 10 neuropsychiatric symptoms: delusions, hallucinations, depression/dysphoria, anxiety, apathy, euphoria, irritability/lability, disinhibition, agitation/aggression, and aberrant motor behavior[36,] • Conducted by an interviewer/rater (ie, trained health care professional) • Administered to caregivers	• A screening question is asked about each sub-domain. If the responses indicate problems with a particular sub-domain of behavior, all the questions about that domain are asked. The interviewer rates the frequency of the symptoms on a 4-point scale, their severity on a 3-point scale, and the distress the symptom causes them on a 5-point scale • Total score ranges from 0 to 120 • Higher scores indicate worse symptoms	• Reported MCID was 8 points[37,]
Alzheimer's Disease Composite Score (ADCOMS)	• Generated from 12 items collected using 3 clinical scales: the CDR-SB, the ADAS-Cog14, and the MMSE.	• Partial least squares regression with a longitudinal clinical decline model was used to identify items from commonly used clinical scales to achieve greater combined sensitivity to change over time [38,39,]	• Literature search did not yield citations supporting MCID values

AD: Alzheimer disease; MCI: mild cognitive impairment; MCID: minimally clinical important difference.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies;
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought;
- Studies with duplicative or overlapping populations were excluded.

REVIEW OF EVIDENCE

Aducanumab

In January 2024, Biogen announced that they were discontinuing the development and commercialization of aducanumab and it will not be discussed further.

Lecanemab

The clinical development program of lecanemab includes 3 studies that are summarized in Table 3.

Table 3. Summary of the Clinical Development Program for Lecanemab

Trial	NCT	Phase	Description	N	Design	Status
Study 201 (Study 1 in the prescribing label)	NCT01767311	2	Dose regimen-finding trial in early AD (ie, MCI due to AD and mild AD dementia).	856	DB RCT	Core: 18 months (completed and published) OLE: Up to 5 years[48,49,]
Clarity AD (Study 301, study 2 in the prescribing label)	NCT03887455	3	Phase 3 confirmatory study in early AD (ie, MCI due to AD and mild AD dementia).	1795	DB RCT	Core: 18 months (completed and published)[50,] OLE: up to 2 years (ongoing)
AHEAD 3-45 Study	NCT04468659	3	Phase 3 study to assess if lecanemab can slow accumulation of amyloid, tau, and prevent cognitive decline in cognitively unimpaired individuals (ie, preclinical AD): intermediate amyloid (20 to 40 centiloids) and elevated amyloid (>40 centiloids)	1400	DB RCT	Ongoing

AD: Alzheimer disease; DB: double-blind; MCI: mild cognitive impairment;NCT: national clinical trial;; OLE: open label extension; RCT: randomized controlled trial.

Systematic Reviews

Several systematic reviews have been published.[46,47,48,49,] They include the lecanemab RCTs described and evaluated in the following section and therefore will not be discussed further.

Randomized Controlled Trials

Lecanemab was approved by the FDA on January 6, 2023 under the accelerated approval pathway based on reduction in amyloid plaque. The accelerated approval was converted to traditional approval in July 2023 based on results of the Clarity AD trial.

Study 201 (study 1 in the prescribing label) was a dose-finding double-blind, placebo-controlled trial. Trial characteristics and results are summarized in Tables 4 to 6. . The trial included an 18-month placebo-controlled treatment period, and a safety follow-up period of 3 months after the final dose. For the placebo-controlled period, patients were randomized to placebo or one of 5 lecanemab dosing regimens, including the FDA approved dosing regimen of 10 mg/kg biweekly. The primary endpoint was change from baseline on a weighted composite score called Alzheimer's Disease Composite Score (ADCOMS) consisting of selected items from the CDR-SB, Mini-Mental State Examination (MMSE), and Alzheimer's Disease Assessment Scale – Cognitive 13-Item Scale (ADAS-Cog 13) at week 53. Lecanemab had a 64% likelihood of 25% or greater slowing of progression on the primary endpoint relative to placebo at week 53, which did not meet the prespecified success criterion of 80%. Change from baseline in brain amyloid plaque as measured by ^{18}F-florbetapir PET and quantified by a composite standard uptake value ratio (SUVR) that was assessed in a subset of patients at week 79 and serves as the endpoint to support accelerated approval. Treatment with lecanemab 10 mg/kg every 2 weeks reduced amyloid beta plaque levels in the brain, producing reductions in PET SUVR compared to placebo at both weeks 53 and 79 ($p<.001$). The magnitude of the reduction was time- and dose-dependent. During an off-treatment period (range from 9 to 59 months; mean of 24 months), SUVR and centiloid values began to increase with a mean rate of increase of 2.6 centiloids/year. However, treatment difference relative to placebo at the end of the double-blind, placebo-controlled period was maintained.

Study 301 (Clarity AD, study 2 in the prescribing label) was a multicenter, randomized, double-blind, placebo-controlled trial comparing 10 mg/kg biweekly lecanemab (n=898) to placebo (n=897). Trial characteristics and results are summarized in Tables 4 to 6. The study included an 18-month (78-week) placebo-controlled period and a safety follow-up period of 3 months after the final dose. There were 235 sites across 13 countries in North America, Europe, Australia, and Asia. Participants met criteria for either MCI due to AD or mild AD dementia as defined by the 2011 National Institute of Aging-Alzheimer's Association (NIA-AA) framework and were required to have evidence of brain amyloid beta (Aβ) pathology by either visual read of a PET scan or cerebrospinal fluid (CSF) assessment of t-tau/$A\beta_{1-42}$. Participants had a baseline MMSE score of 22 to 30 and a CDR global score of 0.5 or 1.0 with a Memory Box score of 0.5 or greater. The primary efficacy endpoint was the change from baseline in CDR-SB at 18 months. The rate of decline in CDR-SB was statistically significantly slower in the lecanemab group. Change from baseline at 18 months in amyloid burden on PET as measured in centiloids in the subgroup tested and change from baseline at 18 months in the ADAS-Cog 14 score, change from baseline at 18

months in the ADCOMS, and change from baseline at 18 months in the Alzheimer's Disease Cooperative Study–Activities of Daily Living Scale for Mild Cognitive Impairment (ADCS-MCI-ADL) score, were all statistically significant favoring lecanemab. Table 5 includes quantitative results. Subgroup analyses for the primary and secondary cognitive outcomes were performed for demographic and baseline characteristics, including apolipoprotein E (ApoE). Treatment comparisons favored lecanemab in all subgroups across the outcome measures tested except for the CDR-SB outcome in ApoE ε4 homozygous participants which favored placebo (n=132 vs 136 in placebo vs lecanemab). While results for ADAS-Cog 14 and ADCS-ADL-MCI did favor lecanemab in the ApoE ε4 homozygous subgroup, the effect size was attenuated compared to ApoE ε4 noncarriers and ε4 heterozygotes.[45,52,50,]

Safety

In study 201, amyloid-related imaging abnormalities (ARIA) was observed in about 12% (20/161) of individuals treated with lecanemab 10 mg/kg biweekly compared to 5% (13/245) in the placebo arm. Respective incidences of ARIA with edema or effusions (ARIA-E) were 10% (16/161) versus 1% (2/245) and ARIA with cerebral microhemorrhages, cerebral macrohemorrhages, or superficial siderosis (ARIA-H) was 6% (10/161) versus 5% (12/245). Symptomatic ARIA occurred in 3% (5/161) of individuals treated with lecanemab. Clinical symptoms associated with ARIA resolved in 80% of patients during the period of observation. The incidence of ARIA was higher in ApoE ε4 homozygotes than in heterozygotes and noncarriers among individuals treated with lecanemab. Of the 5 individuals treated with lecanemab who had symptomatic ARIA, 4 were ApoE ε4 homozygotes, 2 of whom experienced severe symptoms. While the recommendations on management of ARIA do not differ between ApoE ε4 carriers and noncarriers, as per the label, consider testing for ApoE ε4 status to inform the risk of developing ARIA when deciding to initiate treatment with lecanemab.[50,]

In Study 301 (Clarity AD), deaths were reported in 0.7% of the participants in the lecanemab group versus 0.8% in the placebo group. ARIA was observed in 21% (191/898) of individuals treated with lecanemab compared to 9% (84/897) of individuals who received placebo. Symptomatic ARIA occurred in 3% (29/898) of individuals treated with lecanemab. Serious symptoms associated with ARIA were reported in 0.7% (6/898) of individuals treated with lecanemab. ARIA-E was observed in 13% (113/898) of individuals treated with lecanemab compared with 2% (15/897) on placebo. ARIA-H was observed in 17% (152/898) of individuals treated with lecanemab compared with 9% (80/897) on placebo. Clinical symptoms resolved in 92% of individuals with symptomatic ARIA-E and in 73% of individuals with symptomatic ARIA-H within the period of observation. Intracerebral hemorrhage (greater than 1 cm in diameter) was reported in 0.7% (6/898) of individuals on lecanemab compared to 0.1% (1/897) on placebo. Infusion-related reactions were reported in 26% (237/898) of individuals treated with lecanemab compared to 7% (66/897) of patients on placebo. ARIA incidence was higher in ApoE ε4 homozygotes (45% on lecanemab vs 22% on placebo) compared to heterozygotes (19% on lecanemab vs 9% on placebo) and noncarriers (14% on lecanemab vs 4% on placebo). Of the individuals treated with lecanemab who experienced symptomatic ARIA, 45% were ApoE ε4 homozygotes, 41% were heterozygotes, and 14% were noncarriers. Serious events of ARIA occurred in 3% of ApoE ε4 homozygotes, and approximately 1% of heterozygotes and noncarriers.[50,52,]

In the open label extension of Study 301, there were 3 deaths related to ARIA for which a role for lecanemab cannot be ruled out. Two of the deaths were associated with a cerebral

hemorrhage that occurred in ApoE ε4 homozygous individuals with underlying severe cerebral amyloid angiopathy (CAA), 1 of which also was administered tissue plasminogen activator.[52,]

Table 4. Summary of Key Study Characteristics

Study	Country	Design	Sites	Duration	Participants	Interventions	
						Active	Comparator
Study 201 (Study 1 in the prescribing label)[50,51,]	Multinational (US, Canada, EU, UK, Asia)	RCT	169	78-months (79-week double-blind, placebo-controlled period, followed by an open-label extension period for up to 260 weeks)	• 50 to 90 years of age • Confirmed presence of amyloid pathology • MCI or mild dementia as defined by the 2011 NIA-AA framework[a] with evidence of brain Aβ pathology by either visual read of a PET scan or CSF assessment of Aβ1-42. Participants were also required to have: ○ CDR global score of 0.5 or 1.0 ○ Memory Box score of 0.5 or greater ○ MMSE score of ≥22 ○ Objective impairment in episodic memory as indicated by at least 1	Participants randomized[c] to lecanemab • 2.5 mg biweekly (n=52) • 5 mg biweekly (n=89) • 10 mg biweekly (n=152) • 5 mg monthly (n=48) • 10 mg monthly (n=246)	Placebo (n=238); pooled for concurrent arms

Study	Country	Design	Sites	Duration	Participants	Interventions	
					standard deviation below age-adjusted mean in the WMS-IV LMII subscale • Primary clinical endpoint: Change from baseline in ADCOMS at week 53.[b] • Secondary endpoints: brain amyloid plaque content, pharmacokinetics, and immunogenicity • Clinical efficacy endpoints were exploratory		
Clarity AD; Study 301 (Study 2 in the prescribing label)[50, 52, 45, 53,]	Multinational (US, Australia, Canada, China, France, Germany, Italy, Japan, Korea, Russia, Singapore, Spain, Sweden, United Kingdom)	RCT	235	78-week placebo-controlled period, with safety follow-up period of 3 months	• 50 to 90 years of age • AD with confirmed presence of amyloid pathology and mild cognitive impairment (62%) or mild dementia stage of disease (38%) • CDR global score of 0.5 or 1.0 and a Memory Box score of 0.5 or greater • MMSE score of ≥22 and ≤30 • Objective impairment in episodic memory	Lecanemab 10 mg/kg biweekly, n=898	Placebo n=897

Study	Country	Design	Sites	Duration	Participants	Interventions	
					• 69% ApoE ε4 carriers; 31% were ApoE ε4 non-carriers • Median age 72 years (range of 50 to 90) • 52% women • 1381 (77%) White; 303 (17%) Asian; 47 (3%) were Black		

ApoE ε4: *apolipoprotein E ε4*; AD: Alzheimer disease; ADCOMS: Alzheimer's Disease Composite Score; CDR: Clinical Dementia Rating; CSF: cerebrospinal fluid; MCI: mild cognitive impairment; MMSE: Mini-Mental State Examination; NIA-AA: National Institute on Aging-Alzheimer's Association; PET: positron emission tomography; RCT: randomized controlled trial; WMS-IV LMII: Wechsler-Memory Scale-IV Logical Memory II

[a] Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease[10,11,]

[b] Change from baseline in brain amyloid plaque as measured by 18F-florbetapir PET and quantified by a composite standard uptake value ratio (SUVR) was assessed in a subset of patients at week 53 and week 79 and serves as the endpoint to support accelerated approval.

[c] Randomization stratified by clinical subgroups (MCI due to Alzheimer's disease and mild Alzheimer's disease dementia), ApoE ε4 carrier status (carrier or non-carrier), and ongoing treatment with concurrent medications for treatment of Alzheimer's disease

Table 5. Summary of Pivotal Trial Results for Clinical Outcomes

Study 201		
Clinical Outcomes at Week 79[51,50,]	**Lecanemab 10 mg biweekly**	Placebo
ADCOMS		
N at baseline	152	238
Baseline score	0.373	0.370
n at week 79	79	160
LS mean change from baseline at week 79 (±SE)	0.136 (±0.022)	0.193 (±0.017)
Difference from placebo (90% CI)	-0.057 (-0.102 to -0.013)	NA
p-value	.03	NA
CDR-SB		
N at baseline	152	238
Baseline score	2.97	2.89
n at week 79	84	161
LS mean change from baseline at week 79 (±SE)	1.10 (±0.21)	1.50 (±0.16)

Study 201		
Difference from placebo (90% CI)	-0.40 (-0.82 to 0.03)	NA
p-value	.13	NA
ADAS-Cog13		
N at baseline	152	237
Baseline score	22.06	22.56
n at week 79	79	158
LS mean change from baseline at week 79 (±SE)	2.59 (±0.81)	4.90 (±0.62)
Difference from placebo (90% CI)	-2.31 (-3.91 to -0.72)	NA
p-value	.02	NA
Study 301 (Clarity AD)		
Clinical Outcomes at week 79[52,50,45,53,]		
CDR-SB		
N at baseline	859	875
Baseline score	3.17	3.22
n at week 79	714	757
Mean change from baseline at week 79	1.21	1.66
Difference from placebo (%)	-0.45 (-27%)	NA
p-value	<.001	NA
ADAS-Cog13		
N at baseline	854	872
Baseline score	24.45	24.37
n at week 79	703	738
Mean change from baseline at week 79	4.140	5.581
Difference from placebo (%)	-1.442 (-26%)	NA
p-value	<.001	NA
ADCOMS		
Mean change from baseline at week 79	0.164	0.214
Difference from placebo (%)	-0.05 (-24%)	NA
p-value	<.001	NA
ADCS-MCI-ADL		
Baseline score	41.2	40.9

Study 201		
Mean change from baseline at week 79	-3.5 (-37%)	-5.5
Difference from placebo (%)	2.0	NA
p-value	<.001	NA
EQ-5D-5L (subject)		
Difference vs Placebo (%)	2.0 (-49%)	NA
95% CI	0.65 to 3.4	NA
QOL-AD (subject)		
Difference vs Placebo (%)	0.66 (-56%)	NA
95% CI	0.24 to 1.1	NA
Zarit Burden Interview		
Difference vs Placebo (%)	-2.2 (-38%)	NA
95% CI	-3.2 to -1.2	NA

ADAS-Cog13: Alzheimer's Disease Assessment Scale-Cognitive 13-Item Scale; ADCOMS: Alzheimer's Disease Composite Score; ADCS-ADL-MCI: Alzheimer's Disease Cooperative Study-Activities of Daily Living-Mild Cognitive Impairment; CDR-SB: Clinical Dementia Rating Sum of Box; CI: confidence interval; EQ-5D-5L, European Quality of Life-5 Dimensions 5-Level version; LS: least square; MMSE: Mini-Mental State Examination; NA: not applicable; QOL-AD, Quality of Life in Alzheimer's Disease; SE: standard error.
Results presented above are based on ITT analysis which was defined as all randomized subjects who received at least one dose of study treatment and excluding data collected after March 20, 2019.

Table 6. Summary of Pivotal Trial Results for Biomarker Outcomes

Study 201		
Biomarkers Endpoints[a] [51,50,]	**Lecanemab 10 mg biweekly**	**Placebo**
Amyloid PET Composite SUVR		
N	44	98
Mean baseline	1.373	1.402
Adjusted mean change from baseline at week 79	-0.306	0.004
Difference from placebo	-0.310	NA
p-value	<.001	NA
Amyloid Beta PET Centiloid		
N	44	98
Mean baseline	78.0	84.8
Adjusted mean change from baseline at week 79	-72.5	1.0
Difference from placebo	-73.5	NA
p-value	<.001	NA
Plasma Aβ42/40[2]		

Study 201		
N	43	88
Baseline	0.0842	0.0855
Adjusted mean change from baseline at week 79	0.0075	0.0021
Difference from placebo	0.0054	NA
p-value	.0036	NA
Plasma p-tau181 (pg/mL)[b]		
N	84	179
Mean baseline	4.6474	4.435
Adjusted mean change from baseline at week 79	-1.1127	0.0832
Difference from placebo	-1.1960	NA
p-value	<.0001	NA
Study 301 (Clarity AD)[45,]		
Amyloid burden on PET (centiloids)		
N	354	344
Adjusted mean change from baseline at week 78	-55.48	3.64
Difference from placebo (95% CI)	-59.12 (-62.64 to -55.60)	NA
p-value	<.0001	

CI: confidence interval; NA: not applicable; PET: positron emission tomography; p-Tau; phosphorylated tau; SUVR: standard uptake value ratio
Results as reported in the prescribing label. N is the number of patients with baseline value.
[a] P-values were not statistically controlled for multiple comparisons.
[b] As per the label, plasma Aβ42/40 and plasma p-tau181 results should be interpreted with caution due to uncertainties in bioanalysis

The purpose of Tables 7and 8 is to display notable limitations in the evidence. This information is synthesized as a summary of the body of evidence following each table and provides the conclusions on the sufficiency of the evidence supporting the position statement. Key limitations in study relevance include limited duration of follow-up to assess clinical benefits and harms. Key design and conduct limitations of phase 3 studies include the potential for partial unblinding due to adverse events, questions regarding the clinical significance of the effect on cognition and function, and generalizability to broader clinical populations and real world settings.

Table 7. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-up[e]
Study 201 (Study 1 in the prescribing label)[50,51,]	4. Study population not representative of intended use			2. Physiologic measures, not validated surrogates;	1. Not sufficient duration for benefit; 2. Not sufficient

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-up[e]
	(under-representation of African American and Hispanic patients)			5. Clinical significant difference not prespecified; 6. Clinical significant difference not supported.	duration for harms.
Study 301 (Study 2 in the prescribing label) [52,50,45,]	4. Study population not representative of intended use (under-representation of African American patients)				1. Benefit beyond 18 months uncertain; 2. Long-term impact of ARIA uncertain although majority resolved.

ARIA: amyloid-related imaging abnormalities.
The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.
[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4.Not the intervention of interest.
[c] Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.
[d] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not establish and validated measurements; 5. Clinical significant difference not prespecified; 6. Clinical significant difference not supported.
[e] Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

Table 8. Study Design and Conduct Limitations

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
Study 201 (Study 1 in the prescribing label)[50,51,]				1. High loss to follow-up or missing data	3. Power not based on clinically important difference	
Study 301 (Study 2 in the prescribing label) [52,50,45,]		1. Potential for unblinding due to infusion reactions; sensitivity analysis				

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
		were performed and indicated potential unblinding was not likely to change conclusions				

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.
[b] Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.
[c] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
[d] Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).
[e] Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.
[f] Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated.

Section Summary: Lecanemab

For individuals with early AD (MCI or mild dementia due to AD) who receive lecanemab, the evidence includes 2 double-blind RCTs with sample sizes of 390 and 1795. Both trials reported an approximately 27% statistically significantly slower rate of decline for the primary cognitive and functional outcome (ADCOMS for Study 201; CDR-SB for Study 301) for lecanemab versus placebo. In the phase 3 Study 301 (Clarity AD), the rate of decline for all 4 secondary cognitive and functional outcomes were statistically significant favoring lecanemab. Measures of quality of life and caregiver burden also favored lecanemab. ARIA was observed in 21% (191/898) of patients treated with lecanemab compared to 9% (84/897) on placebo. Symptomatic ARIA occurred in 3% (29/898) of patients treated with lecanemab. The incidence of ARIA was higher in ApoE ε4 homozygotes.

SUPPLEMENTAL INFORMATION

Clinical Input From Physician Specialty Societies And Academic Medical Centers

While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

2024 Input

Clinical input was sought to help determine whether the use of lecanemab for individuals with early Alzheimer Disease (AD) would provide a clinically meaningful improvement in net health

outcome. In response to requests, clinical input was received from 3 respondents; 1 physician-level response identified through a specialty society; 3 physician-level responses identified through an academic medical center.

For individuals who have early AD who receive lecanemab, clinical input supports this use provides a clinically meaningful improvement in net health outcome with the criteria described.

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

Practice Guidelines and Position Statements
Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

Institute for Clinical and Economic Review
The Institute for Clinical and Economic Review published a report assessing the effectiveness and value of lecanemab for Alzheimer disease on April 17, 2023. The report concluded, "the net health benefits of lecanemab in participants with early AD [Alzheimer Disease] may be small or even substantial, but there remains a possibility of net harm from ARIA [amyloid-related imaging abnormalities], we rate treatment with lecanemab in MCI [mild cognitive impairment] due to AD or mild AD as promising but inconclusive (P/I)." [53,]

U.S. Preventive Services Task Force Recommendations
Not applicable

Ongoing and Unpublished Clinical Trials
Some currently ongoing and unpublished trials that might influence this review are listed in Table 9.

Table 9. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT05738486	Investigating the Effect of Different Donanemab Dosing Regimens on ARIA-E and Amyloid Lowering in Adults With Early Symptomatic Alzheimer's Disease	800	May 2025
NCT04241068[a]	A Study to Evaluate Safety and Tolerability of Aducanumab in Participants With Alzheimer's Disease Who Had Previously Participated in the Aducanumab Studies 221AD103, 221AD301, 221AD302 and 221AD205 (EMBARK)	1696	Aug 2028
NCT05310071[a]	A Study to Verify the Clinical Benefit of Aducanumab in Participants With Early Alzheimer's Disease (ENVISION)	1512	Oct 2026

NCT No.	Trial Name	Planned Enrollment	Completion Date
NCT05508789	Global Study to Investigate Safety and Efficacy of Donanemab in Early Symptomatic Alzheimer's Disease	1500	Apr 2027
NCT01760005[a]	A Phase II/III Multicenter Randomized, Double-Blind, Placebo-Controlled Platform Trial of Potential Disease Modifying Therapies Utilizing Biomarker, Cognitive, and Clinical Endpoints in Dominantly Inherited Alzheimer's Disease (DIAN-TU)	490	Oct 2027
NCT05269394[a]	A Phase II/III Multicenter Randomized, Double-Blind, Placebo-Controlled Platform Trial of Potential Disease Modifying Therapies Utilizing Biomarker, Cognitive, and Clinical Endpoints in Dominantly Inherited Alzheimer's Disease (DIAN-TU)	168	Oct 2027
NCT04468659[a]	AHEAD 3-45 Study: A Placebo-Controlled, Double-Blind, Parallel-Treatment Arm, 216 Week Study to Evaluate Efficacy and Safety of Treatment With BAN2401 in Subjects With Preclinical Alzheimer's Disease and Elevated Amyloid (A45 Trial) and in Subjects With Early Preclinical Alzheimer's Disease and Intermediate Amyloid (A3 Trial)	1400	Feb 2029
NCT05026866	A Study of Donanemab Versus Placebo in Participants at Risk for Cognitive and Functional Decline of Alzheimer's Disease (TRAILBLAZER-ALZ 3)	2600	Nov 2027

NCT: national clinical trial.
[a] Denotes industry-sponsored or cosponsored trial.

CODING

The following codes for treatment and procedures applicable to this policy are included below for informational purposes. This may not be a comprehensive list of procedure codes applicable to this policy.

Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

The code(s) listed below are medically necessary ONLY if the procedure is performed according to the "Policy" section of this document.

CPT/HCPCS	
J0172	Injection, aducanumab-avwa, 2 mg
J0174	Injection, lecanemab-irmb, 1 mg
J0175	Injection, donanemab-azbt, 2 mg

REVISIONS	
07-08-2021	Policy added to the bcbsks.com web site.
08-17-2021	Title changed from "Aducanumab (Aduhelm)" to "Aducanumab (Aduhelm) for Alzheimer Disease"
	Updated Description section
	In Policy section: ▪ Replaced "Aduhelm (aducanumab-avwa) is considered experimental / investigational for all indications, including but not limited to Alzheimer's Disease, as clinical benefit has not been established." With "The use of aducanumab is considered experimental / investigational for all indications, including treatment of Alzheimer's Disease."
	Updated Rationale section
	In the Coding Section: ▪ Remove HCPC Code J3590
	Updated References section
12-2-2021	Updated Description Section
	Updated Rationale Section
	Updated References Section
12-22-2022	Updated Description Section
	Updated Rationale Section
	Updated Policy Guideline Section • Removed Policy Guidelines "The product label recommends that a baseline brain magnetic resonance imaging (MRI) within 1 year must be done prior to initiating treatment due to the risk of amyloid-related imaging abnormalities (ARIA). Subsequently, MRI should be repeated prior to the 7th and 12th infusions. If radiographic severe ARIA-hemorrhage (ARIA-H) is observed, treatment may be continued with caution only after a clinical evaluation and a follow-up MRI demonstrates radiographic stabilization (i.e., no increase in size or number of ARIA-H)."
	Updated Coding Section ▪ Deleted J3490 ▪ Added J0172

REVISIONS	
	Updated References Section
Posted June 27, 2023 Effective July 27, 2023	Updated Title to "Monoclonal Antibodies for Treatment of Alzheimer Disease"
	Updated Description Section
	Updated Policy Section ▪ Added "and lecanemab" to policy statement
	Updated Rationale Section
	Updated Coding Section ▪ Removed ICD-10 Diagnoses Box ▪ Added J0174
	Updated References Section
Posted 08-23-2024 Effective 09-01-2024	Updated Description Section
	Updated Policy Section ▪ Added New Section A: A. Lecanemab may be considered medically necessary for individuals if they meet ALL of the following criteria: 1. Initiation of therapy: a. Meets criteria for mild cognitive impairment (MCI) or mild dementia stage of Alzheimer disease (AD) (see Policy Guidelines); b. Presence of amyloid beta pathology (see Policy Guidelines); c. Access to an appropriate healthcare delivery model (see Policy Guidelines); d. No contraindication(s) to MRI scanning; e. MRI scan completed within previous 12 months which does not show: i. Evidence of a non-AD dementia; ii. Evidence of significant pathological findings on brain MRI (see Policy Guidelines); f. Does not have: i. Concurrent neurological condition(s), other than MCI or AD, contributing to cognitive impairment ii. History of stroke, transient ischemic attacks or seizures within 12 months prior to initiating treatment with lecanemab; iii. Bleeding disorder that is not under adequate control (including a platelet count <50,000 or international normalized ratio [INR] >1.5); g. If the individual is receiving anticoagulant therapy, anticoagulant status should be optimized and individual should be on a stable dose for 4 weeks prior to initiating treatment with lecanemab; h. Not receiving another anti-amyloid monoclonal antibody (e.g., aducanumab). i. Is prescribed in accordance with the U.S. Food and Drug Administration (FDA) approved prescribing label (see Policy Guidelines). ▪ Added Section B: B. Incremental reauthorization for lecanemab may be considered medically necessary for individuals if they meet all the following criteria: 1. Continuation of therapy: a. Has not progressed to moderate or severe dementia; b. Has received MRI during treatment with lecanemab according to schedule recommended in FDA label to monitor for amyloid-related imagining abnormalities (ARIA) (see Policy Guidelines) which does not show: i. ARIA of the severity that meets recommendations for dosing interruptions provided in FDA label (see Policy Guidelines); ii. Evidence of significant pathological findings on brain MRI (see Policy Guidelines); iii. Evidence of stroke. ▪ Added Section C: Lecanemab is considered experimental / investigational when the above criteria are not met. ▪ Changed Previous Section A to Section D: to read "The use of all other monoclonal antibodies is considered experimental / investigational for all indications, including treatment of Alzheimer's Disease (AD)."

REVISIONS	
	Updated Policy Guideline Section ▪ Added Policy Guidelines A. Aducanumab In January 2024, Biogen announced that the company was discontinuing the development and commercialization of Aduhelm® (aducanumab). Biogen stated that individuals receiving Aduhelm in clinical trials will continue to have it available until May 1, 2024, and individuals receiving it by prescription will have it available until Nov. 1, 2024. B. Lecanemab 1. Recommended Dose Per the label, the recommended dosage is 10 mg/kg that must be diluted then administered as an intravenous infusion over approximately 1 hour, once every 2 weeks. 2. Monitoring The product label of lecanemab recommends that a baseline brain MRI within 1 year must be done prior to initiating treatment due to the risk of ARIA. Subsequently, MRI should be repeated prior to the fifth, seventh, and fourteenth infusions. Follow recommendations for dosing interruptions in individuals with ARIA as specified in the US FDA-approved prescribing label. 3. Boxed Warning The product label includes a boxed warning regarding the risk of ARIA. The warning states that providers should discuss the potential risk of serious adverse events associated with ARIA when deciding to initiate treatment. The warning also states that individuals who are ApoE ε4 homozygotes have a higher incidence of ARIA and testing for ApoE ε4 status should be performed prior to initiation of treatment to inform the risk of developing ARIA. 4. Healthcare Delivery Model An appropriate healthcare delivery model for lecanemab would include care delivered in a setting that may include access to: a. Trained and experienced psychometricians, neuropsychiatrists, neurologists, geriatric psychiatrists and/or geriatricians to diagnose and stage Alzheimer disease (AD); b. Trained and experienced radiologists for MRI interpretation for ARIA-E, ARIA-H, superficial siderosis and micro hemorrhages; c. Protocol for the management of serious and severe ARIA; d. Individuals receiving lecanemab preferably has an informant/care partner as part of discussion for treatment initiation, continuation and monitoring. 5. Diagnosis of Mild Cognitive Impairment or Mild Dementia Lecanemab was evaluated in the pivotal trial called Clarity AD (ClinicalTrials.gov number, NCT03887455). The Clarity AD trial criteria for diagnosis of mild cognitive impairment or mild dementia were as follows: Mild cognitive impairment (MCI) due to AD–intermediate likelihood: a. Meet the National Institute of Aging–Alzheimer's Association (NIA-AA) core clinical criteria for MCI due to AD–intermediate likelihood; b. Have a global Clinical Dementia Rating (CDR) score of 0.5 and a CDR Memory Box score of 0.5 or greater; c. Report a history of subjective memory decline with gradual onset and slow progression over the last 1 year which is corroborated by an informant. Mild AD dementia: a. Meet the NIA-AA core clinical criteria for probable AD dementia; b. Have a global CDR score of 0.5 to 1.0 and a CDR Memory Box score of 0.5 or greater. Other Clarity-AD criteria related to cognitive impairment: a. Mini Mental State Examination (MMSE)* score ≥ 22; b. 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) *Given that the MMSE is copyrighted and is not free to use, responses from clinical input and the criteria from the Veterans Affairs (VA) indicate that the Short Test of Mental Status (STMS > 24), Montreal Cognitive Assessment (MoCA > 15), or Saint Louis University Mental Status (SLUMS) > 16 may be reasonable alternatives when MMSE is not available. 6. Positive amyloid pathology

REVISIONS	
	The Clarity AD trial criteria for positive biomarker for brain amyloid pathology includes at least 1 of the following: a. Positron emission tomography (PET) assessment of imaging agent uptake into brain within 12 months; b. Cerebrospinal fluid (CSF) assessment of t-tau/Aβ[1-42]. 7. Exclusionary pathological findings on MRI The Clarity AD trial criteria excluded individuals with significant pathological findings on brain MRI, including but not limited to: a. more than 4 microhemorrhages (defined as 10 mm or less at the greatest diameter); b. a single macrohemorrhage greater than 10 mm at greatest diameter; c. an area of superficial siderosis; d. evidence of vasogenic edema; e. evidence of cerebral contusion, encephalomalacia, aneurysms, vascular malformations, or infective lesions; f. evidence of multiple lacunar infarcts or stroke involving a major vascular territory, severe small vessel, or white matter disease; g. space occupying lesions; h. brain tumors (however, lesions diagnosed as meningiomas or arachnoid cysts and less than 1 cm at their greatest diameter need not be exclusionary).
	Updated Rationale Section
	Updated References Section
01-28-2025	Updated Description Section
	Updated Coding Section ▪ Added J0175

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