Medical Policy

BlueCross BlueShield Kansas
An Independent licensee of the Blue Cross Blue Shield Association

Title: Monoclonal Antibodies for Treatment of Alzheimer Disease

Professional / Institutional
Original Effective Date: July 08, 2021
Latest Review Date: July 27, 2023
Current Effective Date: July 27, 2023

State and Federal mandates and health plan member contract language, including specific provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage. To verify a member's benefits, contact Blue Cross and Blue Shield of Kansas Customer Service.

The BCBSKS Medical Policies contained herein are for informational purposes and apply only to members who have health insurance through BCBSKS or who are covered by a self-insured group plan administered by BCBSKS. Medical Policy for FEP members is subject to FEP medical policy which may differ from BCBSKS Medical Policy.

The medical policies do not constitute medical advice or medical care. Treating health care providers are independent contractors and are neither employees nor agents of Blue Cross and Blue Shield of Kansas and are solely responsible for diagnosis, treatment and medical advice.

If your patient is covered under a different Blue Cross and Blue Shield plan, please refer to the Medical Policies of that plan.

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

Populations	Interventions	Comparators	Outcomes
mild dementia due to Alzheimer disease)			• 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, patients 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. Two monoclonal antibodies (aducanumab and lecanemab) have been approved by the U.S. Food and Drug Administration under accelerated approval based on the reduction in amyloid beta plaques. Continued approval for this indication may be contingent upon verification of clinical benefit in a confirmatory trial.

OBJECTIVE

The objective of this evidence review is to assess whether treatment with monoclonal antibodies improves the net health outcome in patients 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 CSF 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	• Normal performance within expected range on objective cognitive tests. • Transitional cognitive decline (change	• Performance in the impaired/abnormal range on objective cognitive tests. • Evidence of decline from baseline. • Performs daily life	• Substantial progressive cognitive impairment affecting several domains, and/or neurobehavioral disturbance. • Clearly evident functional	• Progressive cognitive impairment or neurobehavioral changes. • Extensive functional impact on daily life with impairme	• Progressive cognitive impairment or neurobehavioral changes. • Clinical interview may not be possible.

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**
	neurobehavioral symptoms.	from individual baseline within past 1 to 3 years, and persistent for at least 6 months). • Mild neurobehavioral changes may coexist or may be the primary complaint rather than cognitive. • No functional impact on daily life activities.	activities independently, but cognitive difficulty may result in detectable but mild functional impact on the more complex activities of daily life.	impact on daily life, affecting mainly instrumental activities. • No longer fully independent/ requires occasional assistance with daily life activities.	nt in basic activities. • No longer independent and requires frequent assistance with daily life activities.	• Complete dependency due to severe functional impact on daily life with impairment in basic activities, including basic self-care.

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

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. Continued approval for this indication may be contingent upon verification of clinical benefit in confirmatory trial(s).

In July 2021, FDA amended the approved label to emphasize the disease stages studied in the clinical trials. The amended label states, "Treatment with aducanumab should be initiated in patients with MCI or mild dementia stage of disease, the population in which treatment was initiated in clinical trials. There are no safety or effectiveness data on initiating treatment at earlier or later stages of the disease than were studied."

In April 2022, FDA amended the approved label to emphasize that physicians confirm that amyloid beta pathology is present before starting treatment.

The FDA, under the accelerated approval regulations (21 CFR 601.41), requires that Biogen conduct a RCT to evaluate the efficacy of aducanumab compared to an appropriate control for the treatment of AD. The trial should be of sufficient duration to observe changes on an acceptable endpoint in the patient population enrolled in the trial. The expected date of trial completion is August 2029 and final report submission to the FDA by February 2030

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. Continued approval for this indication may be contingent upon verification of clinical benefit in confirmatory trial(s).

The FDA, under the accelerated approval regulations (21 CFR 601.41), requires that Eisai conduct a RCT to evaluate the efficacy of lecanemab compared to an appropriate control for the treatment of AD. The trial should be of sufficient duration to observe changes on an acceptable endpoint in the patient population enrolled in the trial. The expected date of trial completion is September 2022 and final report submission to the FDA by March 2023.

POLICY

The use of aducanumab and lecanemab is considered **experimental / investigational** for all indications, including treatment of Alzheimer's Disease.

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 February 1. 2023.

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 aducanumab and 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 which include 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.

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 U.S. Food and Drug Administration (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 patients 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	• Prespecified severity anchors range from none = 0, questionable =	• Shown to be sufficiently sensitive and specific to detect change

Outcome Measure	Description	Scale	Clinically meaningful difference/Comment
	interview of the patient and a reliable informant or collateral source (e.g., family member) • Scoring requires extensive training and is subject to 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	0.5, mild = 1, moderate = 2 to severe = 3 (the personal care domain omits the 0.5 score) • 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	over time in early symptomatic AD participants[21,] • Average increase in 1 to 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

Outcome Measure	Description	Scale	Clinically meaningful difference/Comment
			impacted by patients' educational achievement, and learning effects are 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	• 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	• Consists of 17 instrumental items (e.g., shopping, preparing meals, using household appliances) and 1 basic item (getting dressed)	• Literature search did not yield citations supporting MCID values • The ADCS-ADL has been used as an endpoint

Outcome Measure	Description	Scale	Clinically meaningful difference/Comment
(ADCS-ADL-MCI)	• Conducted by an interviewer/rater (ie, trained health care professional) • Administered to caregivers	• Total score ranges from 0 to 53 • Lower scores indicate greater severity/functional deterioration	in AD clinical trials[33,34,35,]
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	• Literature search did not yield citations supporting MCID values

Outcome Measure	Description	Scale	Clinically meaningful difference/Comment
		change over time [38,39,]	

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

The clinical development program of aducanumab includes 4 studies that are summarized in Table 3.

Table 3. Summary of the Clinical Development Program for Aducanumab

Trial	NCT	Phase	Description	N	Design	Status
PRIME (Study 3)	NCT01677572	1	Evaluate safety and tolerability of multiple doses of aducanumab in prodromal or mild AD	196	DB RCT	Completed and published[40,]
ENGAGE (Study 301)	NCT02477800	3	Evaluate safety and tolerability of aducanumab in early AD	1647	DB RCT	Completed and published[41, 42,]
EMERGE (Study 302)	NCT02484547	3	Evaluate safety and tolerability of aducanumab in early AD	1638	DB RCT	Completed and published[41, 42,]
EMBARK	NCT04241068	3	Evaluate long-term safety and tolerability of aducanumab in participants enrolled in previous trials of aducanumab (EMERGE, ENGAGE, the LTE of the PRIME study, and EVOLVE)	2400	Open label	Ongoing

AD: Alzheimer disease; DB: double-blind; LTE: long-term extension; NCT: national clinical trial; RCT: randomized controlled trial.

Randomized Controlled Trials

The evidence for aducanumab includes a dose-finding and proof of concept phase 1 trial (PRIME) and 2 phase 3 pivotal trials (ENGAGE [study 301] and EMERGE [study 302]). PRIME was a multicenter, randomized, double-blind, placebo-controlled, dose-ranging, staggered study conducted in the United States with the primary objectives of safety and tolerability. The phase 3 studies were multicenter, global, randomized, double-blind, placebo-controlled studies of identical design with the primary objective of efficacy and safety. In all 3 studies, the diagnosis of AD was confirmed by presence of amyloid pathology measured by [^{18}F]-florbetapir positron emission tomography (PET) imaging. The pivotal trials ensured enrollment of patients at an earlier stage of their disease; MCI due to AD or mild AD dementia based on an entry criteria of baseline Mini-Mental State Examination (MMSE) score of 24 to 30, baseline CDR global score of 0.5 and Repeatable Battery for the Assessment of Neurological Status (RBANS) delayed memory index score ≤85. Per the protocol design, most participants had a diagnosis of MCI due to AD (81.6%), while 18.4% of participants had mild AD dementia. Approximately two-thirds of the study population in the phase 3 trials are *apolipoprotein E* (*ApoE) ε4* carriers. The trial had approximately 90% power to detect a true mean difference of 0.5 in change from baseline CDR-SB at week 78. The range for CDR-SB is 0 to 18, with higher scores indicating greater disease severity.[12,]

The phase 3 studies randomized patients to aducanumab low dose (3 or 6 mg/kg for *ApoE ε4* carriers and noncarriers, respectively), aducanumab high dose (10 mg/kg), or placebo every 4 weeks for 18 months, followed by an optional, dose-blind, long-term extension period. Although aducanumab 10 mg/kg was hypothesized to be the most efficacious dose, due to safety concerns and limited understanding of amyloid-related imaging abnormalities (ARIA), both studies included an initial titration period of up to 6 months to the maximum target dose. At the beginning of the study, *ApoE ε4* carriers were initially titrated up to a maximum of 6 mg/kg in the high-dose group, which was later adjusted to 10 mg/kg. Both pivotal trials were terminated prior to their planned completion. Study endpoints were analyzed based on a prespecified statistical analysis plan. Due to the early termination and consequent administrative censoring, data were missing for up to 45% of patients randomized in the 2 trials. Approximately, 60% of patients had the opportunity to complete week 78 of the trial before the trials were terminated for futility.[12,] Trial characteristics and results are summarized in Tables 4 to 6.

Study 302 (N=1638) met the primary endpoint in patients treated with high-dose aducanumab with an absolute difference of -0.39 in favor of aducanumab on the 18-point CDR-SB scale (a relative 22% less decline in the high dose aducanumab group compared to placebo, p=.0120). The reported MCID is generally considered to be 1 to 2 points on a scale from 0 to 18. [22,] Results in the low-dose aducanumab group were not statistically significant compared with placebo (absolute difference -0.26, relative difference -15%, p=.0901). The prespecified multiplicity adjustment protocol prioritized testing the low dose on the primary endpoint before testing secondary endpoints for the high dose. Therefore, the p values reported in Table 5 should be considered nominal and no statistically valid conclusions can be made for any of the secondary endpoints for either of treatment arms.[43,]

Study 301 (N=1647) did not meet its primary endpoint of a reduction relative to placebo in the CDR-SB score. For the high-dose arm, an absolute difference of 0.03 and a relative difference of 2% favored placebo (p=.8330). For the low-dose arm, an absolute difference of -0.18 and a relative difference of 12% favored aducanumab (p=.8330). Because of the pre-specified plans to

control for type I error for multiple comparisons, no statistically valid conclusions can therefore be made for any of the secondary endpoints.[12,]

Results of the pre-specified exploratory responder analysis were reported. Two thresholds for defining a responder were used: change from baseline in CDR-SB at week 78 ≤ 0.5 or ≤ 1.5. An explanation for choosing these thresholds was not provided or whether these thresholds represent important clinically meaningful change. All participants with missing data at week 78 were classified as non-responders. In study 302, the proportions of responders for placebo versus high dose at week 78 was 18.8% and 25.7%, respectively, (using CDR-SB cutoff ≤ 0.5) and 32.2% and 39.1%, respectively, (using CDR-SB cutoff ≤ 1.5). In study 301, the proportions of responders for placebo versus high dose at week 78 was 25.7% and 20.2%, respectively, (using CDR-SB cutoff ≤ 0.5) and 39.9% and 36.8%, respectively, (using CDR-SB cutoff ≤ 1.5). These results should be considered exploratory and are not statistically robust. Further, the statistical significance of the results in study 302 are not robust to minor recategorization.[44,]

Change in brain amyloid signal was measured by [^{18}F]-florbetapir PET and quantified by a composite standard uptake value ratio (SUVR) in a subset of sites and patients (n=488) at week 78. In study 302, the adjusted mean change from baseline to week 78 relative to placebo showed a dose-dependent reduction in amyloid beta by -0.179 and -0.278 in the low- and high-dose arms, respectively. In study 301, the adjusted mean change from baseline to week 78 relative to placebo showed a dose-dependent reduction in amyloid beta by -0.167 and -0.232 in the low- and high-dose arms, respectively. While aducanumab showed statistically significant dose dependent changes from baseline in amyloid beta plaques, there are no satisfactory data clearly establishing individual changes in amyloid correlate with or predict long term cognitive and functional changes as measured by CDR-SB. The FDA statistical review[43,] reported no patient-level correlation in study 302 between reduction in amyloid plaque and long term clinical change among the high-dose cohort or full 10 mg/kg dosed subgroup.

Change from baseline in markers of downstream AD tau pathophysiology and neurodegeneration were reported for a small subset of patients collected from a voluntary non-directly randomized sample (n=45 in study 302 and n=33 in study 301). While the prescribing label[45,] reports a statistically significant lowering of both phosphorylated tau and total tau in the treatment arms, aducanumab is not known to directly target tau pathways. Therefore, it is difficult to clinically interpret the observed findings on an off-target exploratory biomarker from a small voluntary non-directly randomized sample.

Safety

Data with limited follow-up are available to analyze safety because the phase 3 trials were stopped prematurely due to futility. Pooled safety data from the 2 phase 3 clinical trials showed that about 35% (compared to 3% in the placebo arm) of patients on aducanumab experienced ARIA, whose clinical effects can range from asymptomatic to severe. Although the majority of patients were asymptomatic or had symptoms such as headache, confusion, or dizziness that resolved with temporary stoppage of the drug, 6.2% of participants receiving the high dose of aducanumab discontinued the drug due to ARIA. The incidence of ARIA-edema was higher in *ApoE* ε4 carriers than non-carriers (42% and 20%, respectively). The majority of ARIA-edema radiographic events occurred early in treatment (within the first 8 doses), although ARIA can occur at any time. Among patients treated with a planned dose of aducanumab 10 mg/kg who had ARIA-edema, the maximum radiographic severity was mild in 30%, moderate in 58%, and

severe in 13% of patients (refer to the prescribing label for classification of severity of ARIA). Resolution occurred in 68% of ARIA-edema patients by 12 weeks, 91% by 20 weeks, and 98% overall after detection. Ten percent of all patients who received aducanumab 10 mg/kg had more than 1 episode of ARIA-edema.[46,]

An increase in falling adverse events was observed in the high-dose group as compared to placebo across the 2 phase 3 studies (15% vs. 12%, respectively). The FDA statistical review[43,] reported a hazard ratio of 1.33 (p=.016) suggesting a 33% relative increase in hazard of falling for 10 mg/kg compared to placebo. A quantitative integration of benefit and risk was not done, but if the high dose increases falls it could be a significant risk for the AD population.

Table 4. Summary of Key Study Characteristics

Study; Trial	Country	Design	Sites	Duration	Participants	Interventions	
						Active	**Comparator**

PRIME (Study 3)[47,43,12,]	U.S.	RCT	27	12-month placebo-controlled period followed by LTE	• 50 to 90 years of age
					• Prodromal AD or mild AD dementia as defined by:
					  ○ Positive for brain amyloid pathology as assessed by [^{18}F]-florbetapir PET
					  ○ Baseline MMSE score of 20 to 30
					  ○ Baseline CDR-SB global score of 0.5 or 1
					• Both *ApoE ε4* carriers and *ApoE ε4* noncarriers were enrolled
					• Primary endpoint:
						Aducanumab fixed dose (in mg/kg): 1 (n=31), 3 (n=32), 6 (n=30), 10 (n=32), titration to 10 over 44 weeks (n=23)	Placebo (n=48); pooled for concurrent arms

Study; Trial	Country	Design	Sites	Duration	Participants	Interventions	
						Active	**Comparator**
					Safety and tolerability • Secondary endpoints: brain amyloid plaque content, pharmacokinetics, and immunogenicity • Clinical efficacy endpoints were exploratory		
EMERGE (Study 302) and ENGAGE (Study 301)[47,43,12,]	Global (20 countries)	RCT	348	18-month placebo-controlled period followed by LTE	• 50 to ≤85 years of age • Meet clinical criteria for MCI due to AD or mild AD according to NIA-AA criteria[a] • Early symptomatic AD as defined by: ○ Positive for brain amyloid pathology as assessed by [^{18}F]-florbetapir PET ○ Baseline MMSE score of 24 to 30 ○ Baseline CDR-SB global score of 0.5 ○ RBANS delayed memory	Aducanumab every 4 weeks • Low dose (3 or 6 mg/kg for *ApoE ε4* carriers and noncarriers, respectively) • High dose (10 mg/kg) • No doses administered after March 20, 2019	Placebo

Study; Trial	Country	Design	Sites	Duration	Participants	Interventions	
						Active	Comparator
					index score ≤85 • Both *ApoE ε4* carriers and *ApoE ε4* noncarriers were enrolled • ~80% baseline clinical diagnosis of MCI due to AD and ~20% with a diagnosis of mild AD dementia • Primary endpoint: change from baseline in CDR-SB at week 78 • Secondary endpoints: clinical decline as measured on the MMSE, ADAS-Cog13, and ADCS-ADL-MCI		

AD: Alzheimer disease; ADAS-Cog13: Alzheimer's Disease Assessment Scale-Cognitive 13-Item Scale; ADCS-ADL-MCI: Alzheimer's Disease Cooperative Study-Activities of Daily Living-Mild Cognitive Impairment; *ApoE ε4*: *apolipoprotein E ε4*; CDR: Clinical Dementia Rating; CDR-SB: Clinical Dementia Rating Sum of Box; LTE: long-term extension; MCI: mild cognitive impairment; MMSE: Mini-Mental State Examination; NIA-AA: National Institute on Aging-Alzheimer's Association; PET: positron emission tomography; RBANS: Repeatable Battery for Assessment of Neuropsychological Status; RCT: randomized controlled trial.

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

Table 5. Summary of Pivotal Trial Results for Clinical Outcomes

	EMERGE (302)[47,43,12,]			**ENGAGE (301)[47,43,12,]**		
Clinical Outcomes at Week 78						
	Placebo	Low dose	High dose	Placebo	Low dose	High dose
N	548	543	547	545	547	554
CDR-SB						
Mean baseline score	2.47	2.46	2.51	2.40	2.43	2.40
n at week 78	288	290	299	333	331	295
Change at week 78	1.74	1.47	1.35	1.56	1.38	1.59
Absolute change vs placebo	NA	-0.26	-0.39	NA	-0.18	0.03
Percent change vs placebo	NA	-15%	-22%	NA	-12%	2%
p-value	NA	.0901	.0120	NA	.2250	.8330
MMSE						
Mean baseline score	26.4	26.3	26.3	26.4	26.4	26.4
n at week 78	288	293	299	322	334	297
Change at week 78	-3.3	-3.3	-2.7	-3.5	-3.3	-3.6
Absolute change vs placebo	NA	-0.1	0.6	NA	0.2	-0.1
Percent change vs placebo	NA	3%	-18%	NA	-6%	3%
p-value	NA	.7578	.0493	NA	.4795	.8106
ADAS-Cog13						
Mean baseline score	21.87	Not reported	Not reported	22.48	22.52	22.40
n at week 78	287	289	293	331	332	294
Change at week 78	5.16	4.46	3.76	5.14	4.56	4.55
Absolute change vs placebo	NA	-0.70	-1.40	NA	-0.58	-0.59
Percent change vs placebo	NA	-14%	-27%	NA	-11%	-11%

	EMERGE (302)[47,43,12,]			**ENGAGE (301)[47,43,12,]**		
p-value	NA	.1962	.0097	NA	.2536	.2578
ADCS-ADL-MCI						
Mean baseline score	42.6	42.8	42.5	43.0	42.9	42.9
n at week 78	283	286	295	331	330	298
Change at week 78	-4.3	-3.5	-2.5	-3.8	-3.1	-3.1
Absolute change vs placebo	NA	0.7	1.7	NA	0.7	0.7
Percent change vs placebo	NA	-16%	-40%	NA	-18%	-18%
p-value	NA	.1515	.0006	NA	.1225	.1506

ADAS-Cog13: Alzheimer's Disease Assessment Scale-Cognitive 13-Item Scale; ADCS-ADL-MCI: Alzheimer's Disease Cooperative Study-Activities of Daily Living-Mild Cognitive Impairment; CDR-SB: Clinical Dementia Rating Sum of Box; MMSE: Mini-Mental State Examination; NA: not applicable
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	**EMERGE (302)**			**ENGAGE (301)**			**PRIME (103)**	
Biomarkers Outcomes	Placebo	Low dose	High dose	Placebo	Low dose	High dose	Placebo	High Dose
Amyloid PET								
N	159	159	170	204	198	183	46	31
n at week 78	93	100	109	124	138	112	38	21
Change at week 78	0.014	-0.165	-0.264	-0.003	-0.170	-0.235	0.017	0-.259
Absolute change vs placebo	NA	-0.179	-.0.278	NA	-0.167	-0.232	NA	-0.276
p-value	NA	.001	.001	NA	.001	.001	NA	.001
CSF p-Tau (pg/mL)								
N	28	Not reported	17	15	Not reported	18	Not reported	Not reported
Baseline	72.55	Not reported	100.11	94.53	Not reported	121.81	Not reported	Not reported
Change at week 78	-0.49	Not reported	-22.93	-2.24	Not reported	-13.19	Not reported	Not reported
Absolute change vs placebo	NA	Not reported	-22.44	NA	Not reported	-10.95	Not reported	Not reported

Study	EMERGE (302)			ENGAGE (301)			PRIME (103)	
p-value	NA	Not reported	.0005	NA	Not reported	.0319	Not reported	Not reported
CSF t-Tau (pg/mL)								
N	28	Not reported	17	14	Not reported	16	Not reported	Not reported
Baseline	484.00	Not reported	686.65	592.57	Not reported	618.50	Not reported	Not reported
Change at week 78	-0.39	Not reported	-112.44	-33.26	Not reported	-102.51	Not reported	Not reported
Absolute change vs placebo	NA	Not reported	-112.05	NA	Not reported	-69.25	Not reported	Not reported
p-value	NA	Not reported	.0088	NA	Not reported	.3098	Not reported	Not reported

Results summarized from Prescribing Label[45,]
CSF: cerebrospinal fluid; NA: not applicable; PET: positron emission tomography; p-Tau; phosphorylated tau; t-Tau: total tau.

The purpose of Tables 7 and 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 for phase 3 studies include use of physiologic measures such as amyloid beta and tau proteins and insufficient 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, high loss to follow up or missing data (more than 45% of trials participants did not contribute week 78 data for the primary clinical outcome), and generalizability to broader clinical populations and real world settings. These limitations are explicated below.

Outcomes
Data supporting patient-centric clinical and humanistic outcomes related to cognition (e.g., memory, orientation, judgment/problem-solving, ability to perform cognitive tasks, and everyday functioning) are not interpretable due to conflicting evidence from 2 identical phase 3 RCTs. Study 302 met the primary endpoint of statistically significant change in CDR-SB score in the high-dose arm. The observed magnitude of effect (0.39 points in CDR-SB) is of uncertain clinical benefit. Study 301 failed to meet the same CDR-SB endpoint. In fact, the high-dose arm's change in CDR-SB score was numerically worse than placebo at 78 weeks.[43,] Aducanumab was approved on the basis of statistically significant dose dependent changes in amyloid beta plaques. However, no correlation between reduction in amyloid plaque and change in CDR-SB score was observed in the 10 mg/kg dosed subgroup.[43,] Further, lowering of phosphorylated tau and total tau levels as supportive evidence in the biomarker framework is difficult to interpret as tau levels were an off-target biomarker and results were exploratory from a small voluntary non-directly randomized sample.

Amyloid beta has not been established as a valid surrogate outcome measure to evaluate clinical benefit in patients with MCI or mild dementia due to AD. To establish surrogacy, the relationship

between treatment, a surrogate, and health outcome(s) have to be established. In this case, to establish PET amyloid levels as a surrogate outcome the following would be required: (1) preceding clinical trials demonstrate that the anti-amyloid treatment mitigates cognitive decline; (2) the treatment effect on mitigation of cognitive decline from previous trials is mediated by reduction of amyloid beta levels; (3) the current anti-amyloid treatment has an effect on amyloid beta levels; and (4) amyloid beta levels are associated with cognitive decline. Current evidence demonstrates that aducanumab results in a dose-dependent reduction in amyloid beta while the remaining relationships are not supported by the existing evidence.

Durability and External Validity
The intended double-blind duration of the 2 RCTs was 78 weeks followed by an 18-week safety follow-up period after the final dose. Since the trial was terminated early due to futility, the available data are limited. Due to the early termination and consequent administrative censoring, data were missing for up to 45% of patients at week 78 in the trials. The average follow-up for *ApoE ε4* carriers exposed to a full dose of 10 mg/kg was only 50 weeks rather than 78 weeks. Cognitive decline in MCI due to AD and mild AD generally occurs over years, and thus the follow-up duration may not be sufficient to conclude whether a drug is effective for this disease or whether the safety profile might change with longer follow-up. Further, a statistically significant difference was only reported at week 78 and not any other earlier timepoints. Pooled safety data showed that about 35% of patients on aducanumab experienced ARIA as well as an increase in the risk of falling. While ARIA was detected early by frequent magnetic resonance imaging (MRI) monitoring in the clinical trials, it may be challenging to implement routine monitoring in a real world setting, particularly when it involves patients older than the trial participants. Thus, ARIA may pose greater risks to patients who may be older, have more comorbidities, and are less carefully monitored outside of clinical trials.

Out of 3,285 patients enrolled, less than 1% were Black or African American and 3.2% were Hispanic or Latino. Additionally, the average age was 70 years old although trials allowed for enrollment up to 85 years of age. Given that older African Americans and Latinos are disproportionately more likely to have AD than White Americans and more than one-third of AD patients in the US are over the age of 85, there is limited generalizability of these results to the broader US population.

Study Conduct
Alzheimer's Disease Cooperative Study – Activities of Daily Living – Mild Cognitive Impairment (ADCS-ADL-MCI)

Pivotal trial protocols minimized functional blinding by mandating use of an independent rater who was blinded to patient management (including occurrence of ARIA and subsequent monitoring). However, patients and caregivers could become aware of the occurrence of ARIA due to differential management including additional MRIs and dose modification. The CDR-SB and Alzheimer Disease Cooperative Study-Activities of Daily Living-Mild Cognitive Impairment (ADCS-ADL-MCI) rating scales require more patient and caregiver input and could therefore be susceptible to biased estimates if respondents knew they were on therapy. Further, differential rates of ARIA between study 301 and 302 could have contributed to discordant results because of the impact of differential functional unblinding in the 2 studies.

Table 7. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-up[e]
ENGAGE (Study 301)[47,43, 12,]	4. Study population not representative of intended use			2. Physiologic measures, not validated surrogates; 5. Clinical significant difference not prespecified; 6. Clinical significant difference not supported.	1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.
EMERGE (Study 302)[47,43,12,]	4. Study population not representative of intended use			2. Physiologic measures, not validated surrogates; 5. Clinical significant difference not prespecified; 6. Clinical significant difference not supported.	1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.
PRIME (Study 103)[47,43, 12,]	2. Clinical context is unclear; 4. Study population not representative of intended use			2. Physiologic measures, not validated surrogates; 5. Clinical significant difference not prespecified; 6. Clinical significant difference not supported.	1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

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]
ENGAGE (Study 301)[47,43,12,]				1. High loss to follow-up or missing data	3. Power not based on clinically important difference	
EMERGE (Study 302)[47,43,12,]				1. High loss to follow-up or missing data	3. Power not based on clinically important difference	
PRIME (Study 103)[47,43,12,]					3. Power not based on clinically important difference	

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: Aducanumab

For individuals with early AD (MCI or mild dementia due to AD) who receive aducanumab, the evidence includes 2 RCTs and 1 dose-finding and proof of concept phase I trial. ENGAGE (study 301) and EMERGE (study 302) were identical randomized, double-blind, placebo-controlled studies that enrolled patients with early AD. The majority of patients had a diagnosis of MCI due to AD (81.6%) and approximately two-thirds were *apolipoprotein E ε4* carriers. The primary clinical outcome was change in mean score on the CDR-SB. Both trials were terminated early following a prespecified interim analysis for futility. In study 301, there was no treatment benefit observed in either the high- or low-dose arms at week 78. In study 302, a statistically significant difference in change from baseline in CDR-SB was observed in the high-dose arm (difference vs. placebo -0.39 [95% confidence interval [CI], -0.69 to -0.09]) but not the low-dose arm at week 78. The observed change of 0.39 was well below the range of 1 to 2 points reported as the MCID in published literature. Approval by the FDA was based on the reduction in amyloid beta plaques, which was observed in both trials and at all doses. However, there are no satisfactory data clearly establishing that individual changes in amyloid correlate with or predict long term cognitive and functional changes. In the absence of clinical data convincingly demonstrating a

clinical effect, it cannot be concluded that the observed reduction in amyloid will translate into a clinical benefit to patients. Cognitive decline in early AD generally occurs over years, and thus the follow-up duration may not be sufficient to conclude whether a drug is effective for this disease or whether the safety profile might change with longer follow-up. Pooled safety data showed that about 35% of patients on aducanumab experienced ARIA as well an increase in the risk of falling. A confirmatory, prospective, and adequately powered trial is necessary to assess the net health benefit of aducanumab in patients with early AD.

Lecanemab

The clinical development program of lecanemab includes 3 studies that are summarized in Table 9.

Table 9. 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)	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.

Randomized Controlled Trials

Lecanemab was approved by the FDA on January 6, 2023 under the accelerated approval pathway based on reduction in amyloid plaque. It is proposed that reduction in amyloid plaque is reasonably likely to predict clinical benefit. Subsequent to the accelerated approval, the manufacturer submitted a supplemental Biologics License Application (sBLA) to the U.S. FDA supporting the conversion of the accelerated approval of lecanemab to a traditional approval.

This submission included the results of the Clarity study, a randomized, double-blind, placebo-controlled phase III trial. Results of the Clarity trial have been published.[50,] The sBLA has been granted priority review and FDA is expected to make a decision by July 6, 2023. The FDA is also currently planning to hold an advisory committee to discuss this application but has not yet publicly announced the date of the meeting. At this time, the results of the phase III Clarity trial have not been included in this review as the additional data is being reviewed by the FDA. This review will be updated if lecanemab receives a traditional approval by the FDA.

Current evidence for lecanemab includes a single dose-finding double-blind, placebo-controlled trial (study 201). Trial characteristics and results are summarized in Tables 10 to 12. 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, 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 SUVR 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.[46,51,] While lecanemab showed statistically significant dose dependent changes from baseline in amyloid beta plaques, there are no satisfactory data clearly establishing that individual changes in amyloid correlate with or predict long term cognitive and functional changes as measured by ADCOMS, CDR-SB or ADAS-Cog13.

Safety

Data with limited follow-up are available to analyze safety. In study 1, 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-E were 10% (16/161) versus 1% (2/245) and 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.[46,]

Table 10. Summary of Key Study Characteristics

Study; Trial	Country	Design	Sites	Duration	Participants	Interventions	
						Active	**Comparator**
Study 201 (Study 1 in the prescribing label)[46,51,]	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 standard deviation below age-adjusted mean in the WMS-IV LMII subscale	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; Trial	Country	Design	Sites	Duration	Participants	Interventions	
						Active	Comparator
					• 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		

ApoE ε4: *apolipoprotein E ε4*; 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 11. Summary of Pivotal Trial Results for Clinical Outcomes

Clinical Outcomes at Week 79[51,46,]	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

Clinical Outcomes at Week 79[51,46,]	**Lecanemab 10 mg biweekly**	**Placebo**
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)
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

ADAS-Cog13: Alzheimer's Disease Assessment Scale-Cognitive 13-Item Scale; ADCS-ADL-MCI: Alzheimer's Disease Cooperative Study-Activities of Daily Living-Mild Cognitive Impairment; CDR-SB: Clinical Dementia Rating Sum of Box; CI: confidence interval; LS: least square; MMSE: Mini-Mental State Examination; NA: not applicable; 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 12. Summary of Pivotal Trial Results for Biomarker Outcomes

Biomarkers Endpoints[a51,46,]	**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

Biomarkers Endpoints[a51,46,]	Lecanemab 10 mg biweekly	Placebo
Plasma Aβ42/40[2]		
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

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 13 and 14 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 use of physiologic measures such as amyloid beta and tau proteins and insufficient 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, high loss to follow up or missing data, and generalizability to broader clinical populations and real world settings. These limitations have been explicated in the previous section of aducanumab.

Table 13. 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)[46,51,]	4. Study population not representative of intended use (under-representation of African American and Hispanic patients)			2. Physiologic measures, not validated surrogates; 5. Clinical significant difference not prespecified; 6. Clinical significant difference not supported.	1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

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 14. 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)[46,51,]				1. High loss to follow-up or missing data	3. Power not based on clinically important difference	

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 a single dose-finding RCT (study 201). In this placebo-controlled trial, participants 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 consisting of selected items from the CDR-SB, MMSE, and ADAS-Cog 14 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%. Approval by the FDA was based on the reduction in amyloid beta plaques. Change from baseline in brain amyloid plaque was assessed in a subset of patients at week 79. 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. The magnitude of the reduction was time- and dose-dependent. However, there are no satisfactory data clearly establishing that individual changes in amyloid correlate with or predict long term cognitive and functional changes. In the absence of clinical data convincingly demonstrating a clinical effect, it cannot be concluded that the observed reduction in amyloid will translate into a clinical benefit to patients. Cognitive decline in early AD generally occurs over years, and thus the follow-up duration may not be sufficient to conclude whether a drug is effective for this disease or whether the safety profile might change with longer follow-up. Safety data showed that about 12% of patients on lecanemab experienced ARIA. A confirmatory, prospective, and adequately powered trial is necessary to assess the net health benefit of lecanemab in patients with early AD.

SUPPLEMENTAL INFORMATION
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 aducanumab for Alzheimer disease on August 5, 2021. [52,]The report concluded, "given the certainty that harms can occur in patients treated with aducanumab and uncertainty about benefits, we rate the evidence to be insufficient to determine the net health benefit of aducanumab ("I")." The conclusion about uncertainty of benefits stems from a number of methodologic issues raised in the report that includes use of a phase Ib trial to provide a "second" positive trial as supportive evidence, post-hoc analyses to explain failure of study 301, and role of functional blinding due to amyloid-related imaging abnormalities.

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 15.

Table 15. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT04241068 [a] (EMBARK)	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	169 6	Oct 2023
NCT05310071[a] (ENVISION)[a]	A Study to Verify the Clinical Benefit of Aducanumab in Participants With Early Alzheimer's Disease	1512	Oct 2026
NCT05108922[a] (TRAILBLAZER-ALZ 4)	A Study of Donanemab (LY3002813) Compared With Aducanumab in Participants With Early Symptomatic Alzheimer's Disease (TRAILBLAZER-ALZ 4)	200	Jul 2024
Unpublished			
NCT02434718[a] (PROPEL)	Single and Multiple Ascending Dose Study of Aducanumab (BIIB037) in Japanese Participants With Alzheimer's Disease	21	Dec 2016
NCT03639987[a] (EVOLVE)	A Study of Aducanumab in Participants With Mild Cognitive Impairment Due to Alzheimer's Disease or With Mild Alzheimer's Disease Dementia to Evaluate the Safety of Continued Dosing in Participants With Asymptomatic Amyloid-Related Imaging Abnormalities	52	Jul 2019

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

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
	Updated References Section

REVISIONS	
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

REFERENCES

1. 2021 Alzheimer's disease facts and figures. Alzheimers Dement. Mar 2021; 17(3): 327-406. PMID 33756057
2. Alzheimer's Association. 2021 Alzheimers disease facts and figures. Published 2021. Available at https://www.alz.org/media/Documents/alzheimers-facts-and-figures.pdf. Accessed April 6, 2023.
3. Roberts RO, Aakre JA, Kremers WK, et al. Prevalence and Outcomes of Amyloid Positivity Among Persons Without Dementia in a Longitudinal, Population-Based Setting. JAMA Neurol. Aug 01 2018; 75(8): 970-979. PMID 29710225
4. Elias-Sonnenschein LS, Viechtbauer W, Ramakers IH, et al. Predictive value of APOE-ε4 allele for progression from MCI to AD-type dementia: a meta-analysis. J Neurol Neurosurg Psychiatry. Oct 2011; 82(10): 1149-56. PMID 21493755
5. Mattsson N, Groot C, Jansen WJ, et al. Prevalence of the apolipoprotein E ε4 allele in amyloid β positive subjects across the spectrum of Alzheimer's disease. Alzheimers Dement. Jul 2018; 14(7): 913-924. PMID 29601787
6. Farrer LA, Cupples LA, Haines JL, et al. Effects of age, sex, and ethnicity on the association between apolipoprotein E genotype and Alzheimer disease. A meta-analysis. APOE and Alzheimer Disease Meta Analysis Consortium. JAMA. Oct 1997; 278(16): 1349-56. PMID 9343467
7. Bekris LM, Yu CE, Bird TD, et al. Genetics of Alzheimer disease. J Geriatr Psychiatry Neurol. Dec 2010; 23(4): 213-27. PMID 21045163
8. Vermunt L, Sikkes SAM, van den Hout A, et al. Duration of preclinical, prodromal, and dementia stages of Alzheimer's disease in relation to age, sex, and APOE genotype. Alzheimers Dement. Jul 2019; 15(7): 888-898. PMID 31164314
9. US Food and Drug Administration. Early Alzheimers disease: developing drugs for treatment guidance for industry. Draft Guidance. Published online Feb 29, 2018. Available at https://www.fda.gov/media/110903/download. Accessed on May 19, 2022
10. Albert MS, DeKosky ST, Dickson D, et al. The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement. May 2011; 7(3): 270-9. PMID 21514249
11. McKhann GM, Knopman DS, Chertkow H, et al. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement. May 2011; 7(3): 263-9. PMID 21514250
12. Combined FDA and Applicant PCNS Drugs Advisory Committee Briefing Document: Peripheral and Central Nervous System (PCNS) Drugs Advisory Committee Meeting-

November 6, 2020. Available at https://www.fda.gov/media/143502/download Accessed April 6, 2023.
13. Reuben DB, Tan ZS, Romero T, et al. Patient and Caregiver Benefit From a Comprehensive Dementia Care Program: 1-Year Results From the UCLA Alzheimer's and Dementia Care Program. J Am Geriatr Soc. Nov 2019; 67(11): 2267-2273. PMID 31355423
14. Gronek P, Balko S, Gronek J, et al. Physical Activity and Alzheimer's Disease: A Narrative Review. Aging Dis. Dec 2019; 10(6): 1282-1292. PMID 31788339
15. Du Z, Li Y, Li J, et al. Physical activity can improve cognition in patients with Alzheimer's disease: a systematic review and meta-analysis of randomized controlled trials. Clin Interv Aging. 2018; 13: 1593-1603. PMID 30233156
16. Gitlin LN, Kales HC, Lyketsos CG. Nonpharmacologic management of behavioral symptoms in dementia. JAMA. Nov 21 2012; 308(19): 2020-9. PMID 23168825
17. Kaduszkiewicz H, Zimmermann T, Beck-Bornholdt HP, et al. Cholinesterase inhibitors for patients with Alzheimer's disease: systematic review of randomised clinical trials. BMJ. Aug 06 2005; 331(7512): 321-7. PMID 16081444
18. Jack CR, Bennett DA, Blennow K, et al. NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease. Alzheimers Dement. Apr 2018; 14(4): 535-562. PMID 29653606
19. US Food and Drug Administration. Draft guidance for industry on Alzheimers disease: developing drugs for the treatment of early stage disease. Published online March 28, 2013. Available at https://isctm.org/public_access/FDAGuidance_AD_Developing_Drugs_Early_Stage_Treatment.pdf. Accessed on April 6, 2023.
20. Liu KY, Schneider LS, Howard R. The need to show minimum clinically important differences in Alzheimer's disease trials. Lancet Psychiatry. Nov 2021; 8(11): 1013-1016. PMID 34087114
21. Cedarbaum JM, Jaros M, Hernandez C, et al. Rationale for use of the Clinical Dementia Rating Sum of Boxes as a primary outcome measure for Alzheimer's disease clinical trials. Alzheimers Dement. Feb 2013; 9(1 Suppl): S45-55. PMID 22658286
22. Andrews JS, Desai U, Kirson NY, et al. Disease severity and minimal clinically important differences in clinical outcome assessments for Alzheimer's disease clinical trials. Alzheimers Dement (N Y). 2019; 5: 354-363. PMID 31417957
23. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res. Nov 1975; 12(3): 189-98. PMID 1202204
24. Chapman KR, Bing-Canar H, Alosco ML, et al. Mini Mental State Examination and Logical Memory scores for entry into Alzheimer's disease trials. Alzheimers Res Ther. Feb 22 2016; 8: 9. PMID 26899835
25. Franco-Marina F, García-González JJ, Wagner-Echeagaray F, et al. The Mini-mental State Examination revisited: ceiling and floor effects after score adjustment for educational level in an aging Mexican population. Int Psychogeriatr. Feb 2010; 22(1): 72-81. PMID 19735592
26. Galasko D, Abramson I, Corey-Bloom J, et al. Repeated exposure to the Mini-Mental State Examination and the Information-Memory-Concentration Test results in a practice effect in Alzheimer's disease. Neurology. Aug 1993; 43(8): 1559-63. PMID 8351011
27. Spencer RJ, Wendell CR, Giggey PP, et al. Psychometric limitations of the mini-mental state examination among nondemented older adults: an evaluation of neurocognitive and

magnetic resonance imaging correlates. Exp Aging Res. 2013; 39(4): 382-97. PMID 23875837
28. Mohs RC, Knopman D, Petersen RC, et al. Development of cognitive instruments for use in clinical trials of antidementia drugs: additions to the Alzheimer's Disease Assessment Scale that broaden its scope. The Alzheimer's Disease Cooperative Study. Alzheimer Dis Assoc Disord. 1997; 11 Suppl 2: S13-21. PMID 9236948
29. Rosen WG, Mohs RC, Davis KL. A new rating scale for Alzheimer's disease. Am J Psychiatry. Nov 1984; 141(11): 1356-64. PMID 6496779
30. Schrag A, Schott JM. What is the clinically relevant change on the ADAS-Cog?. J Neurol Neurosurg Psychiatry. Feb 2012; 83(2): 171-3. PMID 22019547
31. McDougall F, Edgar C, Mertes M, et al. Psychometric Properties of the Clinical Dementia Rating - Sum of Boxes and Other Cognitive and Functional Outcomes in a Prodromal Alzheimer's Disease Population. J Prev Alzheimers Dis. 2021; 8(2): 151-160. PMID 33569561
32. Vellas B, Bateman R, Blennow K, et al. Endpoints for Pre-Dementia AD Trials: A Report from the EU/US/CTAD Task Force. J Prev Alzheimers Dis. Jun 2015; 2(2): 128-135. PMID 26247004
33. Bullock R, Touchon J, Bergman H, et al. Rivastigmine and donepezil treatment in moderate to moderately-severe Alzheimer's disease over a 2-year period. Curr Med Res Opin. Aug 2005; 21(8): 1317-27. PMID 16083542
34. Tariot PN, Solomon PR, Morris JC, et al. A 5-month, randomized, placebo-controlled trial of galantamine in AD. The Galantamine USA-10 Study Group. Neurology. Jun 27 2000; 54(12): 2269-76. PMID 10881251
35. Doody RS, Thomas RG, Farlow M, et al. Phase 3 trials of solanezumab for mild-to-moderate Alzheimer's disease. N Engl J Med. Jan 23 2014; 370(4): 311-21. PMID 24450890
36. Cummings J. The Neuropsychiatric Inventory: Development and Applications. J Geriatr Psychiatry Neurol. Mar 2020; 33(2): 73-84. PMID 32013737
37. Howard R, Phillips P, Johnson T, et al. Determining the minimum clinically important differences for outcomes in the DOMINO trial. Int J Geriatr Psychiatry. Aug 2011; 26(8): 812-7. PMID 20848576
38. Wang J, Logovinsky V, Hendrix SB, et al. ADCOMS: a composite clinical outcome for prodromal Alzheimer's disease trials. J Neurol Neurosurg Psychiatry. Sep 2016; 87(9): 993-9. PMID 27010616
39. Tahami Monfared AA, Houghton K, Zhang Q, et al. Staging Disease Severity Using the Alzheimer's Disease Composite Score (ADCOMS): A Retrospective Data Analysis. Neurol Ther. Mar 2022; 11(1): 413-434. PMID 35099758
40. Sevigny J, Chiao P, Bussière T, et al. The antibody aducanumab reduces Aβ plaques in Alzheimer's disease. Nature. Sep 01 2016; 537(7618): 50-6. PMID 27582220
41. Salloway S, Chalkias S, Barkhof F, et al. Amyloid-Related Imaging Abnormalities in 2 Phase 3 Studies Evaluating Aducanumab in Patients With Early Alzheimer Disease. JAMA Neurol. Jan 01 2022; 79(1): 13-21. PMID 34807243
42. Budd Haeberlein S, Aisen PS, Barkhof F, et al. Two Randomized Phase 3 Studies of Aducanumab in Early Alzheimer's Disease. J Prev Alzheimers Dis. 2022; 9(2): 197-210. PMID 35542991
43. FDA Pre-Recorded Presentation Slides for the November 6, 2020: Meeting of the Peripheral and Central Nervous System Drugs Advisory Committee. Available at https://www.fda.gov/media/143504/download. Accessed on April 6, 2023.

44. Center for Drug Evaluation and Research. Statistical Review. Application Number: 761178orig1s000. Available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2021/761178Orig1s000StatR_Redacted.pdf. Accessed April 6, 2023.
45. Prescribing Label: ADUHELM (aducanumab-avwa) injection, for intravenous use Available at https://www.biogencdn.com/us/aduhelm-pi.pdf. Accessed on April 6, 2023.
46. Prescribing Label for LEQEMBI (lecanemab-irmb) injection, for intravenous use. Available at https://www.leqembi.com/-/media/Files/Leqembi/Prescribing-Information.pdf?hash=3d7bf1a2-5db2-4990-8388-81086f415676. Accessed on April 6, 2023.
47. Biogen Presentation for the November 6, 2020: Meeting of the Peripheral and Central Nervous System Drugs Advisory Committee. Available at https://www.fda.gov/media/143577/download. Accessed on April 6, 2023.
48. Swanson CJ, Zhang Y, Dhadda S, et al. A randomized, double-blind, phase 2b proof-of-concept clinical trial in early Alzheimer's disease with lecanemab, an anti-Aβ protofibril antibody. Alzheimers Res Ther. Apr 17 2021; 13(1): 80. PMID 33865446
49. McDade E, Cummings JL, Dhadda S, et al. Lecanemab in patients with early Alzheimer's disease: detailed results on biomarker, cognitive, and clinical effects from the randomized and open-label extension of the phase 2 proof-of-concept study. Alzheimers Res Ther. Dec 21 2022; 14(1): 191. PMID 36544184
50. van Dyck CH, Swanson CJ, Aisen P, et al. Lecanemab in Early Alzheimer's Disease. N Engl J Med. Jan 05 2023; 388(1): 9-21. PMID 36449413
51. Summary Review for Leqembi (lecanemab) Application Number: 761269Orig1s000. Center for Drug Evaluation and Research. Available at https://www.accessdata.fda.gov/drugsatfda_docs/summary_review/2023/761269Orig1s000SumR.pdf. Accessed on April 6, 2023.
52. Aducanumab for Alzheimers Disease: Effectiveness and Value- Final Evidence Report and Meeting Summary. Institute for Clinical and Economic Review (ICER). Available at https://icer.org/wp-content/uploads/2020/10/ICER_ALZ_Final_Report_080521.pdf Accessed on April 6, 2023.
53. Lecanemab for Early Alzheimers Disease Final Evidence Report April 17, 2023. Available at https://icer.org/wp-content/uploads/2023/04/ICER_Alzheimers-Disease_Final-Report_For-Publication_04172023.pdf. Accessed on April 17, 2023.

OTHER REFERENCES

1. Blue Cross and Blue Shield of Kansas Internal Medicine Liaison Committee; August 2021, June 2023.