Medical Policy

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Title: Aducanumab (Aduhelm) for 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: • 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

DESCRIPTION

Alzheimer disease 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 (A-β), referred to as amyloid plaques are considered a hallmark of the disease. Beta-amyloid monomers lead to formation of beta oligomers and fibrils and are deposited as plaques and then interact with tau fibrils, leading to formation of neuro-fibrillatory tangles. These pathophysiological changes and clinical manifestations of Alzheimer disease are progressive and occur along a continuum, and

accumulation of A-β may begin 20 years or more before symptoms arise. Aducanumab is a human IgG1 anti-A-β antibody targeting amyloid aggregates. The drug is administered by intravenous infusion every 4 weeks. Binding of antibody is intended to lead to clearance of amyloid from the brain. On June 7, 2021, the U.S. Food and Drug Administration approved Aduhelm (aducanumab) for the treatment of Alzheimer disease. It was approved under accelerated approval based on reduction in A-β plaques observed in patients treated with aducanumab. Continued approval for this indication may be contingent upon verification of clinical benefit in confirmatory trial.

OBJECTIVE

The objective of this evidence review is to assess whether treatment with aducanumab 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 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 Alzheimer disease 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 Alzheimer disease dementia, and the number is projected to reach over 12 million by 2050.[1,]

Pathophysiology

The pathologic hallmarks of Alzheimer disease are extracellular deposits of beta-amyloid (A-β), 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 Alzheimer disease is not well understood. Generally referred to as "amyloid hypothesis", it is believed that aggregation of A-β oligomers in the brain leads to amyloid plaques and 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 Alzheimer disease are older age, genetics, and family history. Of these, increasing age has the largest known impact on risk of developing Alzheimer disease. While several genes have been found to increase the risk of Alzheimer disease, the ε4 allele of the apolipoprotein E (*ApoE*) gene is the strongest known genetic risk factor.[4,5,]Having 1 copy of the gene is associated with a 2- to 3-fold increase in developing Alzheimer disease while 2 copies of the gene may increase risk of Alzheimer disease by as much as 15 times.[6,]Approximately two-thirds of pathology-confirmed Alzheimer disease 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 Alzheimer disease cases.[7,]

The pathophysiological changes and clinical manifestations of Alzheimer disease are progressive and occur along a continuum, and accumulation of A-β may begin 20 years or more before symptoms arise.[8,] 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 Alzheimer disease from an initial stage characterized by the appearance of abnormal Alzheimer disease 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 such as those of aducanumab. The phase 3 randomized controlled trials 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 Alzheimer disease outlined in the Food and Drug Administration (FDA) guidance for industry pertaining to developing drugs for treatment of early Alzheimer disease.[9,]

Many tests are available in the market to detect the underlying core pathology such use of certain biomarkers in the cerebrospinal fluid (CSF) (e.g., decreased A-β 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 A-β confirmation that are currently in development in the US. CSF tests and amyloid PET tracers are routinely used in the enrollment of participants in contemporary Alzheimer disease studies.[10,]

Current Treatment

Current treatment goals for patients with Alzheimer disease 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, etc.).[11,] Non-pharmacologic treatments include physical activity[12,13,] 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).[14,] Currently FDA-approved drugs for Alzheimer 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 associated with significant side effects.[14,15,]

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 may be the primary complaint rather than cognitive. • No functional impact on daily life activities.	• 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.

Adapted from Table 6, Jack et al (2018)[16,]

[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 Aβ or associated pathologic state (CSF $A\beta_{42}$, or $A\beta_{42}/A\beta_{40}$ 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 investigators 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.
CSF: cerebrospinal fluid; FDG: fluorodeoxyglucose; MCI: mild cognitive impairment; MRI: magnetic resonance imaging; PET: positron emission tomography.

REGULATORY STATUS

In June 2021, aducanumab (Aduhelm; Biogen) was approved by the U.S. FDA for treatment of Alzheimer disease. This indication was approved under accelerated approval based on reduction in A-β plaques observed in patients treated with aducanumab. 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 Biogen conduct a randomized, controlled trial to evaluate the efficacy of aducanumab-avwa compared to an appropriate control for the treatment of Alzheimer disease. 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.

POLICY

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

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).

RATIONALE

This evidence review has been updated with searches of the PubMed database. The most recent literature update was performed through June 16, 2021.

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 one 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.

EARLY ALZHEIMER DISEASE

Clinical Context and Therapy Purpose

The purpose of aducanumab is to provide a treatment option that is an alternative to or an improvement on existing therapies for patients with early Alzheimer disease (mild cognitive impairment [MCI] or mild dementia due to Alzheimer disease).

The question addressed in this evidence review is: Does the use of aducanumab improve the net health outcome in patients with early Alzheimer disease (MIC or mild dementia due to Alzheimer disease)?

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

Populations

The relevant population of interest are individuals with early Alzheimer disease(MCI or mild dementia due to Alzheimer disease).

Interventions

The therapy being considered is aducanumab. It is a human IgG1 anti-beta-amyloid (A-β) monoclonal antibody selective for A-β aggregates, including soluble oligomers and insoluble fibrils, but not monomers, as demonstrated in a variety of biochemical and structural analyses. Binding of aducanumab to aggregated A-β promotes the removal of amyloid from the brain, through a microglia-mediated phagocytosis mechanism.

Comparators

The following practice is currently being used to treat early Alzheimer disease. Currently approved Alzheimer disease treatments include the cholinesterase inhibitors donepezil, rivastigmine, and galantamine, and the N-methyl-D-aspartate antagonist memantine. None of these agents address 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 Alzheimer disease, treatment for mild to moderate Alzheimer disease 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).[17,] 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.[18,] 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.[19,]

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 Alzheimer disease 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 variability among ethnicity and languages • Cost/licensing requirements for usage • There are total of 6 domains (first 3 for cognition and last 3 for functioning) • Memory • Orientation • Judgment/problem-solving • Community affairs • Home/hobbies • Personal care	• 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) • 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	• Shown to be sufficiently sensitive and specific to detect change over time in early symptomatic Alzheimer disease participants[20,] • Average increase in 1 to 2 points is indicative of a clinically meaningful decline[21,] • For MCI and mild Alzheimer disease, differences of 0.98 and 1.63 points represents clinically meaningful change[19,]
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[22,] • Takes 5 to 8 minutes to administer	• 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[21,] • For MCI and mild Alzheimer disease, differences of 1.26 and 2.32 points

Outcome Measure	Description	Scale	Clinically meaningful difference/Comment
	• 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		represents clinically meaningful change[19,] • 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 observed[23,24,25,26,] • 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[27,28,] • 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 (i.e., trained health care professional) • Administered to patient	• Scores range from 0 to 85 • Higher scores indicated greater severity	• MCID in mild Alzheimer disease is 3 points[29,] • Low sensitivity to detect a change in MCI due to Alzheimer disease[30,31,]
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 (i.e., trained health care professional).	• 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 in Alzheimer disease clinical trials[32,33,34,]

Outcome Measure	Description	Scale	Clinically meaningful difference/Comment
	• Administered to caregivers.	• Total score ranges from 0 to 53 • Lower scores indicate greater 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[35], • Conducted by an interviewer/rater (i.e., 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 indicates worse symptoms	• Reported MCID was 8 points[36],

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

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 Alzheimer disease	196	DB RCT	Completed and published[37,]
ENGAGE (Study 301)	NCT02477800	3	Evaluate safety and tolerability of aducanumab in early Alzheimer disease	1647	DB RCT	Completed and unpublished
EMERGE (Study 302)	NCT02484547	3	Evaluate safety and tolerability of aducanumab in early Alzheimer disease	1638	DB RCT	Completed and unpublished
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

DB: double-blind; LTE: long-term extension; 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 Alzheimer disease 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 Alzheimer disease or mild Alzheimer disease 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 Alzheimer disease (81.6%), while 18.4% of participants had mild Alzheimer disease 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.[10,]

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 was missing for up to 45% of patients randomized in the 2 trials. Approximately, 60 percent of patients had the opportunity to complete week 78 of the trial before the trials were terminated for futility.[10,] Trial characteristics and results are summarized in Tables 4 to 6.

Study 302 (N=1638 randomized patients) 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 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. [21,] Results of responder analysis describing proportion of individuals who achieved a predefined level of improvement was not reported. Results in the low-dose aducanumab group were not statistically significant compared with placebo (absolute difference -0.26, relative difference -15%, p=.0901) and therefore no statistically valid conclusions can be made for any of the secondary endpoints for either of treatment arms.

Study 301 (N=1647 randomized patients) did not meet its primary end point 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.[10,]

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, adjusted mean change from baseline to week 78 relative to placebo showed a dose-dependent reduction in A-β by -0.179 and -0.278 in the low- and high-dose arms respectively. In study 301, adjusted mean change from baseline to week 78 relative to placebo showed a dose-dependent reduction in A-β 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 A-β 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[38,] reported no 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. In the absence of clinical data convincingly demonstrating a clinical effect, it cannot be concluded that observed reduction in amyloid will translate into a clinical benefit to patients.

Change from baseline in markers of downstream Alzheimer disease 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[39,] reports a statistical 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 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.[39,]

An increase in falling adverse events was observed in the high-dose as compared to placebo across the 2 phase 3 studies (15% vs. 12%, respectively). FDA statistical review[38,] 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 Alzheimer disease population.

Table 4. Summary of Key Study Characteristics

Study; Trial	Country	Design	Sites	Duration	Participants	Interventions	
						Active	**Comparator**
PRIME (Study 3)[40,38,10,]	U.S.	RCT	27	12-month placebo-controlled period followed by LTE	• 50 to 90 years of age • Prodromal Alzheimer disease or mild Alzheimer disease dementia as defined by ○ Positive for brain amyloid pathology as assessed by [18F]-florbetapir PET ○ Baseline MMSE score of 20 to 30	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)

Study; Trial	Country	Design	Sites	Duration	Participants	Interventions	
					○ Baseline CDR global score of 0.5 or 1 • Both ApoE ε4 carriers and ApoE ε4 noncarriers were enrolled. • Primary endpoint: Safety and tolerability • Secondary endpoints: brain amyloid plaque content, pharmacokinetics, and immunogenicity • Clinical efficacy endpoints were exploratory		
EMERGE (Study 302/) and ENGAGE (Study 301)[40,38,10,]	Global (20 countries)	RCT	348	18-month placebo-controlled period followed by LTE	• 50 to ≤85 years of age • Early symptomatic Alzheimer disease as defined by ○ Positive for brain amyloid pathology as assessed by [18F]-florbetapir PET ○ Baseline MMSE score of 24 to 30 ○ Baseline CDR global score of 0.5 ○ RBANS delayed memory index score ≤ 85 • Both ApoE ε4 carriers and ApoE ε4 noncarriers were enrolled. • ~80% baseline clinical diagnosis of	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	
					MCI due to Alzheimer disease and ~20% with a diagnosis of mild Alzheimer disease 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		

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; MMSE: Mini-Mental State Examination; PET: positron emission tomography; RBANS: Repeatable Battery for Assessment of Neuropsychological Status.

Table 5. Summary of Pivotal Trial Results for Clinical Outcomes

Study	EMERGE (302)[40,38,10,]			ENGAGE (301)[40,38,10,]		
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 n at week 78 Change at week 78 Absolute change vs placebo Percent change vs placebo p-value	 2.47 288 1.74 NA NA NA	 2.46 290 1.47 -0.26 -15% .0901	 2.51 299 1.35 -0.39 -22% .0120	 2.40 333 1.56 NA NA NA	 2.43 331 1.38 -0.18 -12% .2250	 2.40 295 1.59 0.03 2% .8330
MMSE Mean baseline score n at week 78 Change at week 78	 26.4 288 -3.3 NA	 26.3 293 -3.3 -0.13% .7578	 26.3 299 -2.7 0.6	 26.4 322 -3.5 NA	 26.4 334 0.2 -6% .4795	 26.4 297 -0.1 3% .8106

Study	EMERGE (302)[40,38,10,]			ENGAGE (301)[40,38,10,]		
Absolute change vs placebo Percent change vs placebo p-value	NA NA		-18% .0493	NA NA		
ADAS-Cog13 Mean baseline score n at week 78 Change at week 78 Absolute change vs placebo Percent change vs placebo p-value	21.87 287 5.16 NA NA NA	Not reported 289 4.46 -0.70 -14% .1962	Not reported 293 3.76 -1.40 -27% .0097	22.48 331 5.14 NA NA NA	22.52 332 4.56 -0.58 -11% .2536	22.40 294 4.55 -0.59 -11% .2578
ADCS-ADL-MCI Mean baseline score n at week 78 Change at week 78 Absolute change vs placebo Percent change vs placebo p-value	42.6 283 -4.3 NA NA NA	42.8 286 -3.5 0.7 -16% .1515	42.5 295 -2.5 1.7 -40% .0006	43.0 331 -3.8 NA NA NA	42.9 330 -3.1 0.7 -18% .1225	42.9 298 -3.1 0.7 -18% .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 n at week 78 Change at week 78 Absolute change vs placebo p-value	159 93 0.014 NA NA	159 100 -0.165 -0.179 0.001	170 109 -0.264 -0.278 0.001	204 124 -0.003 NA NA	198 138 -0.170 -0.167 .001	183 112 -0.235 -0.232 .001	46 38 0.017 NA NA	31 21 -0.259 -0.276 .001
CSF p-Tau (pg/mL) N Baseline	28 72.55	-	17 100.11	159 4.53	-	181 21.81	-	-

Study	EMERGE (302)			ENGAGE (301)			PRIME (103)	
Change at week 78 Absolute change vs placebo p-value	-0.49 NA NA		-22.93 -22.44 .0005	-2.24 NA NA		-13.19 -10.95 .3019		
CSF t-Tau (pg/mL) N Baseline Change at week 78 Absolute change vs placebo p-value	 28 484.00 -0.39 NA NA	-	 17 686.65 -112.44 -112.05 .0088	 14 592.57 -33.26 NA NA	-	 16 618.50 -102.51 -69.25 .3098	-	-

Results summarized from Prescribing Label[39,]
CSF: cerebrospinal fluid; NA: not applicable; PET: positron emission tomography; p-Tau; phosphorylated tau; t-Tau: total tau.

The purpose of the 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 A-β 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 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 statistical significant change in CDR-SB score in the high-dose arm. However, the magnitude of observed statistical significant difference are not supported by a responder analysis describing proportion of individuals who achieved a predefined level of improvement. 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.[38,] Aducanumab was approved on the basis of statistically significant dose dependent changes in A-β plaques. However, no correlation between reduction in amyloid plaque and change in CDR-SB score was observed in the 10 mg/kg dosed subgroup.[38,] 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.

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 was missing for up to 45% of patients at week 78 in the trials. The average follow-up

for *ApoE ε4* carriers exposed to full dose of 10 mg/kg was only 50 weeks rather than 78 weeks. Cognitive decline in MCI due to Alzheimer disease and mild Alzheimer disease 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 statistical 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 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 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.

Study Conduct

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 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 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)			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)			2. Physiologic measures, not validated surrogates; 5. Clinical significant difference not prespecified; 6. Clinical significant		1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-up[e]
			difference not supported.		
PRIME (Study 103)	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)			2. Evidence of selective reporting	1. High loss to follow-up or missing data	3. Power not based on clinically important difference	
EMERGE (Study 302)			2. Evidence of selective reporting	1. High loss to follow-up or missing data	3. Power not based on clinically important difference	
PRIME (Study 103)					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: Early Alzheimer Disease

For individuals with early Alzheimer disease (MCI or mild dementia due to Alzheimer disease) 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 Alzheimer disease. The majority of patients had a diagnosis of MCI due to Alzheimer disease (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 A-β 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 Alzheimer disease 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 Alzheimer disease.

Summary of Evidence

For individuals with early Alzheimer disease (MCI or mild dementia due to Alzheimer disease) who receive aducanumab, the evidence includes 2 RCTs and 1 dose-finding and proof of concept phase I trial. Relevant outcomes are disease-specific survival, change in disease status, functional outcomes, health status measures, quality of life, and treatment-related mortality and morbidity. ENGAGE (study 301) and EMERGE (study 302) were identical randomized, double-blind, placebo-controlled studies that enrolled patients with early Alzheimer disease. The majority of patients had a diagnosis of MCI due to Alzheimer disease (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% 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 A-β 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 Alzheimer disease 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 Alzheimer disease. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

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 is assessing the effectiveness and value of aducanumab for Alzheimer disease and have released a draft report.[41,] A final report is expected to be released in August 2021. The draft report concludes, "[g]iven 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 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.

U.S. Preventive Services Task Force Recommendations

Not applicable

Ongoing and Unpublished Clinical Trials

Some currently 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			
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	2400	Oct 2023
Unpublished			
NCT02484547[a] (EMERGE)	221AD302 Phase 3 Study of Aducanumab (BIIB037) in Early Alzheimer's Disease	1638	Aug 2019
NCT02477800[a] (ENGAGE)	221AD301 Phase 3 Study of Aducanumab (BIIB037) in Early Alzheimer's Disease	1647	Aug 2019
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

J3490 Unclassified Drugs

ICD-10 Diagnoses

Experimental / Investigational for all diagnoses related to this medical policy.

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

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