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Keeping up with the everchanging specialty drug market: Alzheimer's disease

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According to the National Institute of Health, Alzheimer's disease is the seventh leading cause of death and the most common cause of dementia in older adults in the United States. Currently more than 6.2 million Americans over the age of 64 have been diagnosed with Alzheimer's disease. That number is expected to more than double by the year 2050.[5]

6.2M+

Americans over the age of 64 have been diagnosed with Alzheimer's disease.

Alzheimer's disease is a neurodegenerative disorder, with progressive and irreversible destruction of neurons leading to loss of cognitive function and memory. Although many complex brain changes are thought to contribute to the development of Alzheimer's disease, during the early stages of the disease there is an abnormal build-up of proteins that form beta-amyloid containing plaques and tau-containing neurofibrillary tangles.[6,12] A period of 10 to 20 years exists between the pre-symptomatic phase of Alzheimer's disease and the emergence of symptoms. Mild cognitive impairment (MCI) refers to the earliest symptomatic stage of cognitive impairment where functional capacity is relatively preserved. Dementia, on the other hand, is defined as cognitive impairment that affects daily function sufficient to impair independence.[6]

The presence of Alzheimer's disease-specific antemortem biomarkers in the setting of clinical characterization can aid in establishing a level of certainty in the diagnosis of Alzheimer's disease. Detection of abnormal beta-amyloid protein in the brain can be done directly through positron emission tomography (PET) imaging using tracers or indirectly by measuring the levels of beta-amyloid 42 in the cerebrospinal fluid (CSF). In addition, the major components of tau neurofibrillary tangles in the brain, tau and phosphor-tau, can also be detected in the CSF. These biomarkers are used to detect the emergence of Alzheimer's disease in individuals with MCI.[6]

Despite the existence of several FDA-approved therapies for Alzheimer's disease, there is an unmet medical need for treatments that target its underlying pathology. Although multiple investigational anti-beta-amyloid antibodies have been studied over the years, many of these medications have previously failed to demonstrate efficacy and/or safety.[12,13] Current FDA-approved treatments that target Alzheimer's disease dementia include cholinesterase inhibitors such as donepezil, galantamine, and rivastigmine and the N-methyl-D-aspartate (NMDA)-antagonist memantine. These treatments address symptomatic impairment in cognition and global function, and the degree of expected benefit is modest.[13] Biogen's aducanumab-avwa (Aduhelm), approved under the U.S. Food & Drug Administration's accelerated approval program on June 7, 2021, is the first human monoclonal antibody directed against beta-amyloid.[14]

In a Phase 1b double-blind, placebo-controlled, randomized clinical trial conducted by Biogen, aducanumab-avwa showed promising early clinical and biomarker data. The PRIME study (Study 103) involved 165 patients randomized into cohorts of fixed aducanumab-avwa doses or placebo. In this study, patients from the aducanumab-avwa arm (n=28) demonstrated statistically significantly greater reductions in beta-amyloid plaques compared to the placebo arm (n = 42).[7]

Based on the results of the PRIME study, Biogen initiated two identical Phase 3 clinical trials, ENGAGE (Study 301) and EMERGE (Study 302) in 2015. Both double-blind, placebo-controlled, multicenter randomized controlled trials had the objective of establishing effectiveness of aducanumab-avwa. The ENGAGE clinical trial had a population of 1674 patients, and the EMERGE clinical trial had a population of 1638 patients. Both involved randomization of patients 1:1:1 to the low dose aducanumab-avwa, high dose aducanumab-avwa, or placebo group. In March of 2019, Biogen conducted a prespecified interim futility analysis on pooled data from the ENGAGE and EMERGE clinical trials. The results of this analysis demonstrated that aducanumab-avwa failed to meet its objectives, and both Phase 3 and the Phase 1b trials were terminated.[8,9,12]

However, a post-hoc analysis was conducted by Biogen to determine why EMERGE demonstrated statistically significant outcomes while ENGAGE did not. This analysis included an examination of individual study results that included data accrued after the cutoff point for the futility analysis in December of 2018 through the termination of the studies in March of 2019. The findings of this post-hoc analysis conflicted with the result of the prespecified interim futility analysis that had resulted in the termination of the clinical trials. Most notably, positive results were observed in EMERGE (Study 302). Biogen concluded that this was based on variance in the population studied and the treatment received based on a protocol amendment that occurred later in the study.[12]

After examination of Biogen's post-hoc analysis of the data from EMERGE (Study 302), the FDA accepted a Biologics License Application (BLA) for aducanumab-avwa and granted Priority Review. On November 6, 2020, the FDA Peripheral and Central Nervous System (PCNS) advisory committee convened to examine data supporting the approval of aducanumab-avwa for Alzheimer's disease. The advisory committee unanimously voted to not approve aducanumab-avwa on the basis that Study 302 (EMERGE), viewed independently and without regard for Study 301 (ENGAGE), did not provide strong evidence that supports the effectiveness of aducanumab-avwa for Alzheimer's disease.[13]

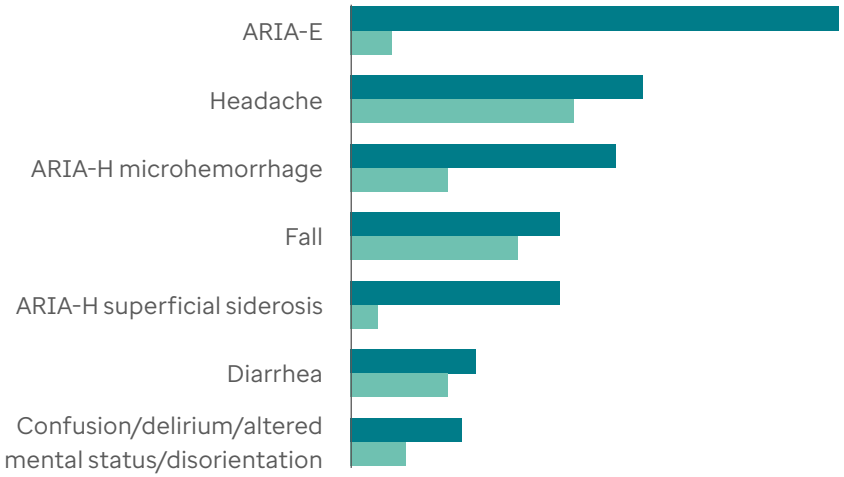
A period of **10 to 20** years exists between the pre-symptomatic phase of Alzheimer's disease and the emergence of symptoms.

Biogen's aducanumab-avwa was subsequently approved under the FDA's Accelerated Approval program on June 7, 2021.[2] Although the FDA originally broadly approved aducanumab-avwa for the treatment of patients with Alzheimer's disease, the approval was revised on July 7, 2021, to reflect the patient population included in the clinical trials, specifically patients with MCI or mild dementia due to Alzheimer's disease. The revised indication further stated that there is no safety or effectiveness data on initiating treatment at earlier or later stages of the disease than were studied. Of note, biomarker evidence of amyloid pathology was required for participation in Biogen's clinical trials, but the FDA label for aducanumab-avwa does not specify that patients treated with aducanumab-avwa should have elevated beta-amyloid, the target of aducanumab-avwa therapy.[3,8,9]

The accelerated approval of aducanumab-avwa was based upon the drug's effect on a surrogate endpoint, namely the reduction of beta-amyloid plaque. According to the FDA, beta-amyloid plaque is a reasonably likely surrogate, and reduction in beta-amyloid plaque is expected, but not established, to predict clinical benefit.[1] Beta-amyloid plaque reduction was an exploratory endpoint in ENGAGE (Study 301) and EMERGE (Study 302). Results from both studies demonstrated statistically significant reductions in beta-amyloid plaques in the low and high dose aducanumab-avwa treatment arms.[8,9] There are currently no clinical trials that have provided substantial evidence that lowered beta-amyloid predicts clinical benefit in Alzheimer's disease.[13]

The FDA label for aducanumab-avwa does not list any contraindications to treatment. However, Amyloid Related Imaging Abnormalities (ARIA) is listed as a warning.[2,3] ARIA represent a spectrum of imaging findings detected on brain MRI and includes both ARIA-E and ARIA-H, caused by vascular edema and brain microhemorrhage, respectively.[11] The biology of ARIA is not well understood, but both ARIA-E and ARIA-H are detected at increased incidence with anti-beta-amyloid monoclonal antibodies, including aducanumab-avwa. There is no systematic data on continued dosing with aducanumab-avwa following detection of radiographically moderate or severe ARIA. In Studies 301 and 302, temporary dose suspension was required for radiographically moderate or severe ARIA-E and radiographically moderate ARIA-H. Permanent discontinuation of dosing was required for radiographically severe ARIA-H. The FDA label specifically notes that enhanced clinical vigilance for ARIA is recommended during initial treatment with aducanumab-avwa, particularly during titration.[3]

The most common adverse effects seen in Studies 301 (ENGAGE) and 302 (EMERGE) included (aducanumab-avwa vs placebo[3]):



Aducanumab-avwa vs. placebo	
35%	3%
21%	16%
19%	7%
15%	12%
15%	2%
9%	7%
8%	4%

Aducanumab-avwa Placebo

Aducanumab-avwa is administered via intravenous infusion every month, with requirements for ARIA surveillance via MRI prior to treatment initiation, the seventh infusion[3], and the twelfth infusion. Confirmatory safety and efficacy data are pending. In March 2020, Biogen initiated a global, open-label, single-arm, Phase 3b clinical trial (EMBARK [NCT04241068]) with approximately 2,400 patients. The primary objective is to assess the long-term safety of aducanumab-avwa at a dose of 10 mg/kg in patients with Alzheimer's disease who were actively participating in aducanumab-avwa clinical trials (PRIME [Phase 1b], EVOLVE [Phase 2], ENGAGE [Phase 3], and EMERGE [Phase 3]) at the time of their early termination in March of 2019. Secondary study objectives of EMBARK include long-term efficacy and long-term effect of aducanumab-avwa on biomarkers and pharmacokinetic endpoints. An additional goal of EMBARK is to gain understanding regarding the effect of prolonged treatment interruption and improve understanding of the durability of aducanumab-avwa's treatment effects.[10]

Aducanumab-avwa was approved under the FDA's Accelerated Approval program.[1,12] Continued approval of aducanumab-avwa for Alzheimer's disease is contingent upon verification of clinical benefit in confirmatory trial(s). If clinical benefit is not verified, the FDA may initiate proceedings to withdraw approval of the drug. However, as per the timeline approved by the FDA, the results of said verification may not be available until the year 2030.[4]

The Optum Specialty Guidance Program is a comprehensive cost management solution targeting high-cost, complex specialty medications covered under the medical benefit, and is backed by specialty clinicians that are continuously monitoring, evaluating, and making recommendations to our health plan clients on the everchanging specialty drug market. As new therapies and evidence are released, Optum works with payers to update and maintain digitized policy guidelines, this allows the program to guide providers to optimal treatment approaches and uses real-time data to address high-cost medical specialty spend while improving the member's continuum of care.

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