NEW DRUG REVIEW

Generic Name: Aducanumab	Brand Name: Aduhelm
Company: Biogen, Eisai	Route: Intravenous Infusion
Therapeutic Area: Neurology	Indication: Alzheimer's disease
Drug Class: Beta-amyloid antibody	M of A: Monoclonal antibody that reduces amyloid beta by binding to the protein.
FDA Status: Approved	WAC: $28,000 per year
Update	April 26, 2022

Place in Therapy:

Current treatment for Alzheimer's disease (AD) is limited to acetylcholinesterase inhibitors and memantine. A meta-analysis of 13 trials found an improvement with acetylcholinesterase inhibitors in the ADAS-Cog Scale score of 2.7 points, which is similar to the six-month decline seen in natural history studies. Acetylcholinesterase inhibitors are mainly used in mild to moderate Alzheimer's disease. Memantine is used for moderate to severe AD dementia. It may also be added to acetylcholinesterase inhibitors.

Due to limitations in current therapy, researchers have been working on new therapies, but advancement has been slow in finding new treatments.

As part of the approval, the FDA is requiring Biogen to conduct a new clinical trial to verify aducanumab's clinical benefit.

Biogen and Eisai discontinued the Phase III ENGAGE (n=945) and EMERGE (n=803) trials, in March 2019, after an interim analysis by an independent data monitoring committee concluded the trials were unlikely to demonstrate that treatment with aducanumab slowed the rate of decline in cognitive and functional status as measured by the CDR-SB score compared to placebo. In October 2019, Biogen and Eisai announced that an analysis of an expanded cohort of patients enrolled in EMERGE (n=1,084) and ENGAGE (n=982), found a slowing in the rate of decline in cognitive and functional status.

The results of EMERGE and ENGAGE were published in a single article in the Journal of Prevention of Alzheimer's Disease. The data presented in the article is the same as has been previously announced and covered in the FDA briefing document for aducanumab created by Biogen with comments by the FDA and the FDA Division of Neurology. The article did not address limitations identified in the FDA statistical analysis of the trials nor add any insights.

Both EMERGE and ENGAGE were 78-week trials with a primary endpoint of change in CDR-SB and had targeted enrollments of over 1,600 patients, but around 900 in each trial completed 78-weeks of treatment. The trials enrolled patients with mild cognitive impairment (MCI) and early Alzheimer's disease.

In the 877 patient EMERGE trial, treatment with the high dose of aducanumab (10mg/kg/day) resulted in a slowing in the decline of the CDR-SB score by 22% compared to placebo. There was no improvement with the low dose (6mg/kg/day). EMERGE also provided evidence to support a dose-dependent relationship and a reduction in beta-amyloid plaques. However, in the 959 patient, Phase III, ENGAGE

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trial, treatment with aducanumab did not slow the decline of the CDR-SB score with either high or low dose compared to placebo.

The most common adverse effects identified in the EMERGE, ENGAGE and a Phase II trial were headache, diarrhea and Amyloid Related Imaging Abnormalities (ARIA). ARIA is a unique crainioswelling from monoclonal antibody therapy against amyloid-beta. While ARIA is seen in over 40% of patients, only 1.5% receiving the highest dose have a severe reaction. The FDA felt that an appropriate warning for ARIA in the labeling would be acceptable.

Several anti-beta amyloid drugs have been evaluated to treat or prevent Alzheimer's disease and failed to demonstrate a benefit. These include solanezumab (Lilly), bapineuzumab (Pfizer and Johnson and Johnson), verubecestat (Merck) and umibecestat (Amgen and Novartis). The FDA agreed with Biogen that molecular differences between aducanumab and the other drugs along with better trial design and patient selection prevents the older trials from showing a class failure.

A presentation by the FDA's Division of Neurology concluded that positive data from Emerge and a Phase II trial provided substantial evidence of effectiveness to support approval of aducanumab. However, a review by the FDA's Office of Biostatistics concluded that a new trial was needed, because of the conflicting evidence seen in EMERGE and ENGAGE. Use of only favorable results in Emerge would lead to a biased conclusion. Because of this, a future non-inferiority trial comparing a new drug to aducanumab would have unclear results. The availability of aducanumab would also hinder recruitment for future Alzheimer's Disease trials, which may be evaluating more efficacious drugs. The FDA Peripheral and Central Nervous System Drugs Advisory Committee overwhelmingly rejected aducanumab due to a lack of evidence to support efficacy.

The American Academy of Neurology (AAN) published guidelines for the use of aducanumab reviewing evidence and providing considerations for use of the drug to treat early symptomatic Alzheimer's disease (AD). The guideline finds current evidence is of uncertain clinical importance and recommends additional trials to define aducanumab's place in therapy and duration of treatment.

1. Though not required by the FDA, AAN suggests that aducanumab be reserved for patients with elevated cerebral amyloid, positive amyloid PET scan and cerebrospinal biomarkers for AD.
2. Aducanumab should be avoided in patients at high risk for adverse effects, including a past a history of symptomatic hemorrhage or current use of anticoagulants.
3. As with the product labeling, an MRI should be done within the first year of treatment and before the seventh and twelfth doses. An MRI is also indicated if amyloid-related imaging abnormalities (ARIA) are suspected. Patients with an Apolipoprotein E4 mutation are at higher risk for ARIA
4. Duration of aducanumab treatment is unknown

Safety:

Amyloid Related Imaging Abnormalities (ARIA) is a unique crainioswelling from monoclonal antibody therapy targeting amyloid-beta. Two types of ARIA have been identified with aducanumab therapy: ARIA with vasogenic edema (ARIA-E), and ARIA with hemorrhage (ARIA-H). ARIA-H consists of cerebral microhemorrhage, superficial siderosis, and cerebral hemorrhage. ARIA was seen in 41.7% of patients in the EMERGE, ENGAGE and a Phase II trials. ARIA was classified as a serious adverse event in 1.5% of patients that received the highest dose (10mg/Kg) of aducanumab.

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Higher doses of aducanumab and the presence of the ApoE epsilon4 allele increase the risk of ARIA.

The most common adverse effects identified in the EMERGE, ENGAGE and a Phase II trial were ARIA-E, headache, ARIA-H microhemorrhage, fall, ARIA-H superficial siderosis, and diarrhea.

News & Analysis:

The FDA approved aducanumab for the treatment of Alzheimer's disease on 6/7/2021. Use of aducanumab was not limited to patients with early Alzheimer's, similar to the patient populations in the ENGAGE and EVOLVE trials. Rather it was approved for use in any patients with Alzheimer's disease. On July 8, 2021, the FDA approved a narrowed indication for aducanumab, submitted by Biogen, to Alzheimer's Disease patients with mild cognitive impairment or mild dementia. The original approved indication was for all Alzheimer's patients regardless of disease severity, despite the late Phase trials only including patients with mild disease.

The prescribing information for aducanumab contains a warning for amyloid-related imaging abnormalities (ARIA). ARIA usually presents as transient, symptomatic swelling in the brain. But some patients may develop headache, confusion, dizziness, vision changes, or nausea with ARIA. In addition to ARIA, the most common adverse effects include headache, fall, diarrhea, and confusion/delirium/altered mental status/disorientation.

An interim futility analysis of data from 1,748 patients found a low likelihood that aducanumab would improve or slow cognition in Alzheimer's patients, so Biogen discontinued both EMERGE and ENGAGE in March 2019. In Fall 2019, Biogen analyzed additional data from 3,285 patients, of which 2,066 had completed the full 18 months of treatment, and found a reduction in cognition reduction compared to placebo in the EMERGE data. The FDA found that if a non-pooled analysis had been used, the EMERGE study would not have met futility criteria. Based on this data Biogen submitted a BLA for aducanumab.

Biogen also offered patients enrolled in EMERGE and EVOLVE continued access to aducanumab. Biogen also continued the long-term extension study for the Phase 1b PRIME study and the EVOLVE safety study.

The FDA Peripheral and Central Nervous System Drugs Advisory Committee voted 0 yes, 10 no and 1 uncertain on whether there was enough evidence to recommend approval of aducanumab for the treatment of Alzheimer's disease in November 2020. The FDA extended the review date for aducanumab by three months to allow additional time to review new data Biogen has submitted to satisfy an FDA information request.

The California Technology Assessment Forum (CTAF), one of ICER's Independent appraisal committee, met to review ICER's report on aducanumab. CTAF heard presentations from ICER on its report and a rebuttal from Biogen. CTAF voted 15 to 0 that the evidence does not support a beneficial effect with aducanumab over supportive care.

The Department of Veterans Affairs will not include aducanumab on its national formulary due to safety and efficacy concerns. Use of the drug is restricted to specific patients when prescribed by dementia experts. Biogen is restricted from promoting the drug to VA prescribers.

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Debate Between the FDA and Its Peripheral and Central Nervous System Drugs Advisory Committee

Three members of the FDA Peripheral and Central Nervous System Drugs Advisory Committee, which reviewed and rejected aducanumab, published an editorial in JAMA to explain why the drug should not be approved. The authors felt that post hoc analysis should not discredit the negative study, since no other trial based on reduction of beta-amyloid has shown a benefit. They also questioned whether the FDA worked too closely with the study sponsor in a reanalysis of the trials. In conclusion, the authors did not feel that a single positive study justified the approval of aducanumab. After aducanumab was approved, three of the members of the Peripheral and Central Nervous System Drugs Advisory Committee resigned in protest, including one of the authors of the JAMA editorial.

The FDA released documents related to the internal discussion on approval of aducanumab. The Office of Neuroscience supported accelerated approval, while the Office of Biostatistics did not. Senior FDA officials agreed with the Office of Neuroscience and approved the drug, based on the results of the higher dose cohort of the EMERGE trial and discounting the results for the ENGAGE trial. They also based their decision on an unreleased analysis of data from aducanumab, lecanemab and donanemab Alzheimer's trials, which demonstrated a relationship for plaque reduction and improved clinical effects.

Three FDA officials involved in the approval of aducanumab defended their action in an editorial in *JAMA Internal Medicine*. The FDA officials argue that a delay in approval would have resulted in loss of brain function of patients who would benefit from early treatment. They felt this was justified due to the demonstrated reduction in amyloid-plaque, which was shown to decrease the decline in cognitive function. Because aducanumab received an accelerated approval, it was judged to meet criteria to likely provide a benefit for a disease without a current treatment. There was no discussion of the decision to approve the drug for all patients and not just those with mild disease, nor the long timeline for a confirmatory study. The editorial also did not discuss the need to verify that a patient has a build-up of amyloid-plaque, since this was also a criteria used in the trial used for approval.

All seven members of the FDA Peripheral and Central Nervous System Drugs Advisory Committee (AdComm), which reviewed and rejected aducanumab, published a Perspective in *NEJM* that questioned the criteria used to justify approval of aducanumab. The AdComm pointed out that approval was based on a reduction of beta-amyloid that was measured through positron-emission tomographic brain imaging. The committee found available clinical evidence from trials to not support lowered beta-amyloid as a prediction of clinical benefit. The AdComm did not find a single positive study as justification for clinical benefit. They also reiterate the FDA's statistical review of EMERGE and ENGAGE failed to find evidence that amyloid changes correlated with cognitive or functional changes. Aducanumab labeling does not require verification of elevated beta-amyloid despite the FDA basing approval on beta-amyloid reduction. This becomes an important issue since almost half of patients with mild cognitive impairment that are being assessed for Alzheimer's disease do not have elevated levels of beta-amyloid.

Four FDA officials involved in the approval of aducanumab supplied a rebuttal to the Peripheral and Central Nervous System Drugs Advisory Committee Perspective in *NEJM* in the same issue of the journal. The FDA officials argue that use of beta-amyloid as a surrogate marker was justified due to more recent studies demonstrating that larger

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decrease in amyloid plaque correlates with the effect on clinical end points. They point out that while earlier studies of amyloid reducing drugs did not demonstrate a clinical benefit, the products used had little or no effects on amyloid plaque. The decision to approve aducanumab under an Accelerated Approval was justified because they judged the drug to be "reasonably likely" to predict clinical benefit". There was no explanation for approval without requiring establishment of amyloid plaque nor the reason for disagreeing with the FDA Biostatistical Review. Data that supports a beneficial response in relation to plaque reduction is not currently published.

Beginning 1/1/2023, Biogen will assume all marketing and development responsibilities for aducanumab. Eisai will just be only paid royalties on sales and no decision-making authority.

Sales of aducanumab have remained low due to questions on efficacy and the drug's price. CMS agreed and in its final decision, will only cover aducanumab for patients participating a CMS, NIH or FDA trial. Health insurers are either not covering the drug or only covering it in a very restricted population. Many top hospitals are not offering aducanumab because of a lack of compelling evidence to support its use.

In April 2022, Biogen withdrew its MAA for aducanumab when interactions with CHMP indicated the committee did not feel current data demonstrated that benefits outweigh risks.

Pharmacoeconomic Impact:

Biogen set the annual price for aducanumab at $28,000 a year, which is much higher than ICER's cost-effectiveness estimates.

ICER provided a final evidence report for aducanumab in early August 2021. In the report ICER found the evidence to be insufficient to support a slowing of cognitive decline in patients with mild disease. The report also stated that efficacy was not shown in patients with moderate to severe disease and no previous amyloid reducing drug trials have shown a benefit in moderate to severe disease. Most of the positive benefit identified in ENGAGE and EMERGE were from post-hoc analyses, so there is a reduction in the applicability of the findings, due to loss of randomization. ICER also noted that ARIA was seen in over a third of patients and questions whether it can be adequately monitored in practice. ICER estimates the cost-effective range of $2,950 to $8,360. ICER warns that care should be taken in the promotion of aducanumab to ensure that patients and families understand that aducanumab may slow the decline in cognition, but it will not improve cognition or quality of life.

An analysis by Harvard estimated cost effective prices of $3,000 for aducanumab and $20,000 for donanemab. The authors calculated the donanemab price based on a Phase II trial that suggested greater efficacy and limited-duration dosing. Neither aducanumab nor donanemab was found to be cost-effective for treating early Alzheimer disease at current and estimated prices.

Other monoclonal antibodies used to treat neurological conditions range in price from under $8,000 per year for migraine prophylaxis to $67,000 to $90,000 for relapsing multiple sclerosis.

In a Viewpoint in *JAMA Internal Medicine*, two editors and an academic physician examined the impact of the aducanumab's cost on Medicare's budget. The authors estimate patient out-of-pocket costs of up to $11,000 per year and the potential of

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increased premiums for Medicare Part B. Medicare expenditure for all drugs covered under Part B drugs was $35 billion in 2018. If just 17% of the 5.8 million Alzheimer patients on Medicare received aducanumab, the cost would be $57 billion per year.

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References

FDA Briefing document

In the 78-week, 959 patient, Phase III, ENGAGE trial, treatment with aducanumab did not slow the decline of the Clinical Dementia Rating-Sum of Boxes (CDR-SB) score with either high or low doses compared to placebo in patients with mild cognitive impairment (MCI) and early Alzheimer's disease. A total of 1,647 participants were randomized and dosed in ENGAGE with 959 completing the full 18 months.

In the 78-week, 877 patient, Phase III, EMERGE trial, treatment with aducanumab resulted in a slowing in the decline of the Clinical Dementia Rating-Sum of Boxes (CDR-SB) score by 22% with the high dose compared to placebo in patients with mild cognitive impairment (MCI) and early Alzheimer's disease. The low dose did not slow the decline in CDR-SB compared to placebo. EMERGE also provided evidence to support a dose-dependent relationship and a reduction in beta-amyloid plaques. A total of 1,638 participants were randomized and dosed in ENGAGE with 877 completing the full 18 months.

The FDA briefing document for aducanumab describes a 12-month, 196 patient dose-ranging, Phase Ib trial, where 154 of 196 patients completed the study. In the trial 32 patients, which included 23 who were ApoE epsilon4 carriers, received the highest dose of 10mg/kg. In this high dose group, treatment with aducanumab reduced beta-amyloid plaques and resulted in a slowing in the decline of cognitive and functional status as measured by the Clinical Dementia Rating-Sum of Boxes (CDR-SB) score and Mini-Mental State Exam (MMSE) compared to placebo. The other doses did not demonstrate a decrease in the rate of decline.

New Analysis of EMERGE and ENGAGE Announcement

In October 2019, Biogen and Eisai announced an analysis of additional data from patients in EMERGE (n=1,084) and ENGAGE (n=982). Additional patients and data were from the period between the December 2018 data cut-off for the interim analysis to March 2019 when the announcement to discontinue the trials was made. 2,066 patients had completed the full 18 months of treatment. A 23% reduction in the rate of decline in cognitive and functional status was found in the patients who received a high dose of aducanumab in EMERGE and in a subset of patients that had sufficient exposure to the high dose in ENGAGE. The FDA found that if a non-pooled analysis had been used, the EMERGE study would not have met futility criteria and continued. Based on this data Biogen decided to submit a BLA for aducanumab to decrease a decline in cognitive and functional status in patients with early Alzheimer's disease.

Discontinuation of EMERGE AND ENGAGE Announcement

Biogen and Eisai discontinued the Phase III ENGAGE (n=945) and EMERGE (n=803) trials, in March 2019, after an interim analysis by an independent data monitoring committee concluded the trials were unlikely to demonstrate that treatment with aducanumab slowed the rate of decline in cognitive and functional status as measured by the Clinical Dementia Rating-Sum of Boxes (CDR-SB) score compared to placebo.

Review by the FDA Department of Neurology and Department of Biostatistics

FDA slide presentation from the Department of Neurology and Department of Biostatistics. A presentation by the FDA's Division of Neurology concluded that positive data from Emerge and a Phase II trial provided substantial evidence of effectiveness to support approval of aducanumab. However, in a review by the FDA's Office of Biostatistics concluded that a new trial was needed, because of the conflicting evidence seen in EMERGE and ENGAGE. Because of this a future non-inferiority trial comparing a new drug to aducanumab would have unclear results. The availability of aducanumab would also hinder recruitment for future Alzheimer's Disease trials, which may be evaluating more efficacious drugs.

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Comments by the Department of Neurology and Department of Biostatistics

Comments for the FDA slide presentation from the Department of Neurology and Department of Biostatistics. A presentation by the FDA's Division of Neurology concluded that positive data from Emerge and a Phase II trial provided substantial evidence of effectiveness to support approval of aducanumab. However, in a review by the FDA's Office of Biostatistics concluded that a new trial was needed, because of the conflicting evidence seen in EMERGE and ENGAGE. Because of this a future non-inferiority trial comparing a new drug to aducanumab would have unclear results. The availability of aducanumab would also hinder recruitment for future Alzheimer's Disease trials, which may be evaluating more efficacious drugs.

Birks J. Cholinesterase inhibitors for Alzheimer's disease. Cochrane Database Syst Rev. 2006 Jan 25;(1):CD005593. doi: 10.1002/14651858.CD005593.

A meta-analysis of 13 trials found an improvement with acetylcholinesterase inhibitors in the ADAS-Cog Scale score of 2.7 points, which is similar to the six-month decline seen in natural history studies.

Arvanitakis Z, Shah RC, Bennett DA. Diagnosis and Management of Dementia: Review. JAMA. 2019 Oct 22;322(16):1589-1599. doi: 10.1001/jama.2019.4782. PMID: 31638686; PMCID: PMC7462122.

Acetylcholinesterase inhibitors are mainly used in mild to moderate Alzheimer's disease. Memantine is used for moderate to severe AD dementia. It may also be added to acetylcholinesterase inhibitors.

Alexander GC, Emerson S, Kesselheim AS. Evaluation of Aducanumab for Alzheimer Disease: Scientific Evidence and Regulatory Review Involving Efficacy, Safety, and Futility. JAMA. 2021 May 4;325(17):1717-1718. doi: 10.1001/jama.2021.3854. PMID: 33783469.

Three members of the FDA Peripheral and Central Nervous System Drugs Advisory Committee, which reviewed and rejected aducanumab, published an editorial in JAMA to explain why the drug should not be approved. The authors felt that post hoc analysis should not discredit the negative study, since no other trial based on reduction of beta-amyloid has shown a benefit. They also questioned whether the FDA worked too closely with the study sponsor in a reanalysis of the trials. In conclusion, the authors did not feel that a single positive study justified the approval of aducanumab.

Lin GA, Whittington MD, Synnott PG, McKenna A, Campbell J, Pearson SD, Rind DM. Aducanumab for Alzheimer's Disease: Effectiveness and Value; Final Evidence Report and Meeting Summary. Institute for Clinical and Economic Review, August 5, 2021.

ICER provided a final evidence report for aducanumab in early August 2021. In the report ICER found the evidence to be insufficient to support a slowing of cognitive decline in patients with mild disease. The report also stated that efficacy was not shown in patients with moderate to severe disease and no previous amyloid reducing drug trials have shown a benefit in moderate to severe disease. Most of positive benefit identified in ENGAGE and EMERGE were from post-hoc analyses, so there is a reduction in the applicability of the findings, due to loss of randomization. ICER also noted that ARIA was seen in over a third of patients and questions whether it can be adequately monitored in practice. ICER estimates the cost-effective range of $2,950 to $8,360. ICER warns that care should be taken in the promotion of aducanumab to ensure that patients and families understand that aducanumab may slow the decline in cognition, but it will not improve cognition or quality of life.

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FDA Application Review Files
BioPharmDrive Summary of FDA Aducanumab Documents

The FDA released documents related to the internal discussion on approval of aducanumab. The Office of Neuroscience supported accelerated approval, while the Office of Biostatistics did not. Senior FDA officials agreed with the Office of Neuroscience and approved the drug, based on the results of the higher dose cohort of the EMERGE trial and discounting the results for the ENGAGE trial. They also based their decision on an analysis of six trials of Alzheimer's drugs that reduce amyloid and demonstrated a relationship for plaque reduction and a beneficial clinical effect. That analysis has not been released and neither was the full statistical review. The files were originally made available on a special internal documents page, but have been moved to the FDA Application Review Files section of the Drug Approval Package: Aduhelm (aducanumab-avwa) page.

July 8, 2021, Update to Aducanumab Labeling

The FDA approved a narrowed indication for aducanumab, submitted by Biogen, to Alzheimer's Disease patients with mild cognitive impairment or mild dementia. The original approved indication was for all Alzheimer's patients regardless of disease severity, despite the late Phase trials only including patients with mild disease.

California Technology Assessment Forum Vote

The California Technology Assessment Forum (CTAF), one of ICER's Independent appraisal committee, met to review ICER's report on aducanumab. CTAF heard presentations from ICER on its report and a rebuttal from Biogen. CTAF voted 15 to 0 that the evidence does not support a beneficial effect with aducanumab over supportive care.

Dunn B, Stein P, Cavazzoni P. Approval of Aducanumab for Alzheimer Disease-the FDA's Perspective. JAMA Intern Med. 2021 Jul 13. doi: 10.1001/jamainternmed.2021.4607. Epub ahead of print. PMID: 34254984.

Three FDA officials involved in the approval of aducanumab defended their action in an editorial in *JAMA Internal Medicine*. The FDA officials argue that a delay in approval would have resulted in loss of brain function of patients who would benefit from early treatment. They felt this was justified due to the demonstrated reduction in amyloid-plaque, which was shown to decrease the decline in cognitive function. Because aducanumab received an accelerated approval, it was judged to meet criteria to likely provide a benefit for a disease without a current treatment. There was no discussion of the decision to approve the drug for all patients and not just those with mild disease, nor the long timeline for a confirmatory study. The editorial also did not discuss the need to verify that a patient has a build-up of amyloid-plaque, since this was also a criteria used in the trial used for approval.

Crosson FJ, Covinsky K, Redberg RF. Medicare and the Shocking US Food and Drug Administration Approval of Aducanumab: Crisis or Opportunity? JAMA Intern Med. 2021 Jul 13. doi: 10.1001/jamainternmed.2021.4610. Epub ahead of print. PMID: 34254992.

In a Viewpoint in *JAMA Internal Medicine,* two editors and an academic physician examined the impact of the aducanumab's cost on Medicare's budget. The authors estimate patient out-of-pocket costs of up to $11,000 per year and the potential of increased premiums for Medicare Part B. Medicare expenditure for all drugs covered under Part B drugs was $35 billion in 2018. If just 17% of the 5.8 million Alzheimer patients on Medicare received aducanumab, the cost would be $57 billion per year.

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Alexander GC, Knopman DS, Emerson SS, Ovbiagele B, Kryscio RJ, Perlmutter JS, Kesselheim AS. Revisiting FDA Approval of Aducanumab. N Engl J Med. 2021 Jul 28. doi: 10.1056/NEJMp2110468. Epub ahead of print. PMID: 34320282.

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Dunn B, Stein P, Temple R, Cavazzoni P. An Appropriate Use of Accelerated Approval - Aducanumab for Alzheimer's Disease. N Engl J Med. 2021 Jul 28. doi: 10.1056/NEJMc2111960. Epub ahead of print. PMID: 34320283.

Four FDA officials involved in the approval of aducanumab supplied a rebuttal to the Peripheral and Central Nervous System Drugs Advisory Committee Perspective in *NEJM* in the same issue of the journal. The FDA officials argue that use of beta-amyloid as a surrogate marker was justified due to more recent studies demonstrating that larger decrease in amyloid plaque correlates with the effect on clinical end points. They point out that while earlier studies of amyloid reducing drugs did not demonstrate a clinical benefit, the products used had little or no effects on amyloid plaque. The decision to approve aducanumab under an Accelerated Approval was justified because they judged the drug to be "reasonably likely" to predict clinical benefit". There was no explanation for approval without requiring establishment of amyloid plaque nor the reason for disagreeing with the FDA Biostatistical Review. Data that supports a beneficial response in relation to plaque reduction is not currently published.

Day GS, Scarmeas N, Dubinsky R, Coerver K, Mostacero A, West B, Wessels SR, Armstrong MJ. Aducanumab Use in Symptomatic Alzheimer Disease Evidence in Focus: A Report of the AAN Guidelines Subcommittee. Neurology. 2022 Apr 12;98(15):619-631. doi: 10.1212/WNL.0000000000200176. Epub 2022 Feb 23. PMID: 35197360; PMCID: PMC9012273.

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Haeberlein SB, Aisen PS, Barkhof F, et al. Two Randomized Phase 3 Studies of Aducanumab in Early Alzheimer's Disease. J Prev Alz Dis 2022; Published online March 18, 2022, http://dx.doi.org/10.14283/jpad.2022.30

In the 78-week, 877 patient, Phase III, EMERGE trial, treatment with aducanumab resulted in a slowing in the decline of the CDR-SB score by 22% with the high dose compared to placebo in patients with mild cognitive impairment (MCI) and early Alzheimer's disease. The low dose of did not slow the decline in CDR-SB compared to placebo. EMERGE also provided evidence to support a dose-dependent relationship and a reduction in beta-amyloid plaques. A total of 1,638 participants were randomized and dosed in ENGAGE with 877 completing the full 18 months by the end of March 2019. In the 78-week, 959 patient, Phase III, ENGAGE trial, treatment with aducanumab did not slow the decline of the CDR-SB score with either high or low doses compared to placebo in patients with MCI and early Alzheimer's disease. A total of 1,647 participants were randomized and dosed in ENGAGE with 959 completing the full 18 months by the end of March 2019.

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