REVIEW

Role of Aducanumab in the Treatment of Alzheimer's Disease: Challenges and Opportunities

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Abstract: Aducanumab is a monoclonal antibody selective for amyloid β (Aβ) aggregates. In June 2021, aducanumab became the first drug underlying the pathophysiology of Alzheimer's disease (AD) approved by the US Food and Drug Administration (FDA), under the accelerated approval pathway. The decision was based on the ability of aducanumab to remove Aβ plaques, without any evidence that the Aβ clearance is correlated with less cognitive or functional decline. This decision has generated a considerable debate in the scientific community, especially because the results from the two Phase 3 trials, EMERGE and ENGAGE, were divergent and, even after the post hoc analysis, the data were insufficient to prove aducanumab efficacy. Moreover, some researchers think that this approval will be an obstacle to the progress and also demonstrated concerns about aducanumab cost and its safety profile. The European Medicines Agency's rejection of aducanumab in December 2021 just brought more controversy over FDA's decision. Now, Biogen is designing the FDA's required confirmatory study, named ENVISION, which should be complete in 2026. Despite the controversy, the aducanumab showed to affect downstream tau pathology, which could open doors for a combination therapy approach for AD (anti-tau and anti-amyloid drug). This review summarizes the clinical development of aducanumab until regulatory agencies' decisions, the available trials data and the controversy over aducanumab approval for AD.

Keywords: anti-Aβ monoclonal antibody, ARIA, clinical trials, European Medicines Agency, Food and Drug Administration, tau protein

Introduction

Alzheimer´s Disease (AD) is a neurodegenerative disorder characterized by progressive loss of memory and cognitive impairment, usually followed by behavioral changes and loss of functional abilities. The World Health Organization recognizes AD as a growing global health concern with a significant impact on individuals, caregivers, and society. By 2060, the number of AD patients is expected to reach 13.8 million, just in the United States (US).[1,2]

Until recently, only four drugs had been approved for AD treatment (donepezil, galantamine, rivastigmine, and memantine).[1] These drugs temporary attenuate symptoms but do not target AD's two main recognized pathological features: extracellular deposits of amyloid β (Aβ) in plaques and intracellular neurofibrillary tangles (comprised of abnormal tau protein).[3,4]

On June 7, 2021, aducanumab (Aduhelm™, Biogen) became the first disease-modifying therapy approved by the US Food and Drug Administration (FDA) and the first AD drug approved since 2003 (memantine).[5] Aducanumab is a monoclonal antibody selective for aggregated forms of Aβ, with demonstrated efficacy in the clearance of brain Aβ plaques.[6] According to the amyloid cascade hypothesis, the extracellular accumulation of Aβ aggregates is the leading cause of synapses dysfunction, neuroinflammation, neuronal loss and is also the trigger of tau pathology.[7] Thus, researchers believe that Aβ clearance by aducanumab is a rational mechanism to slow cognitive decline in AD. However, there is a lack of correlation between the reduction of Aβ plaques and clinical improvements in trials to date.[8–10] The known controversy over the FDA aducanumab approval decision begins here.[11–13]

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Aducanumab was granted accelerated approval by the FDA, a provisional approval for drugs targeting serious diseases that appear to have considerable advantages over current treatment. This decision was based on the surrogate endpoint of Aβ plaques reduction, which the FDA believes to be a biomarker reasonably likely to predict clinical benefit.[5,14] The scientific community has been divided and confounded with this decision once it was based on an unproven biomarker and without data showing clear evidence of clinical efficacy.[11,12,14–17] Furthermore, the approval was taken after the FDA's independent advisory committee recommended against it.[11,18–20] Although the FDA's accelerated approval requires a confirmatory trial to verify clinical efficacy, until 2030, several experts are worried that aducanumab's approval could set a dangerous precedent and lead companies to abandon other targets associated with AD (such as tau protein).[11,13]

In addition, there are also considerable concerns about the cost and the safety of this new drug. Firstly, Biogen set the price of aducanumab at US$ 56,000 per person annually. Secondly, aducanumab had a significantly higher incidence of brain swelling and intracerebral hemorrhages (amyloid-related imaging abnormalities, ARIA) in patients treated with aducanumab.[21] Bearing this last point in mind and the divergent outcomes of clinical trials, the European Medicines Agency (EMA) rejected the marketing authorization for aducanumab on December 17, 2021.[22] Similarly, on December 22, 2021, the Japan's Pharmaceuticals and Medical Devices Agency (PMDA) declined the Aduhelm™ approval.[23,24]

In this review, we first summarize the aducanumab path until drug agencies' conclusions. Secondly, we analyze the trials data available in detail and, finally, explore the controversy and the challenges surrounding its approval.

Aducanumab: Selective Anti-Aβ Antibody

Over the last 25 years, several drugs targeting Aβ have failed to show clinical efficacy in trials, including five anti-Aβ antibodies: bapineuzumab, solanezumab, crenezumab, ponezumab, and gantenerumab.[25,26] Thus, supporters of the amyloid hypothesis placed high hopes on aducanumab.

Aducanumab is part of a new generation of monoclonal anti-Aβ antibodies that specifically target Aβ aggregates. These aggregates, in particular the soluble oligomers, appear to be the most neurotoxic forms of Aβ, whereas the monomeric Aβ possibly have a neuroprotective role in the brain.[10,27–29] Hence, the high selectivity of aducanumab for Aβ aggregates, including soluble oligomers and insoluble fibrils, constitutes a major advantage over previous anti-Aβ antibodies.[30] Studies demonstrated that aducanumab's binding promotes the clearance of Aβ aggregates through the activation of microglial phagocytosis.[6] Besides the clearance, aducanumab is the only antibody that disrupts the Aβ aggregation process by inhibiting the secondary nucleation (formation of oligomers on the fibril surface) due to its affinity and binding stoichiometry to Aβ aggregates.[19,31] These reasons made aducanumab the most promising drug for AD of the last decade.

Clinical Development and Regulatory History Overview

Aducanumab's path to approval was slightly unconventional, due to a close collaboration between the sponsor (Biogen) and the FDA, during the whole process. The aducanumab clinical program had three essential studies to evaluate efficacy: PRIME, ENGAGE and EMERGE, also known as studies 103, 301, and 302, respectively.[19,32] Next, we explore the clinical development of aducanumab until regulatory agencies' decisions (Figure 1).

Clinical Trials and the FDA Collaboration

Aducanumab moved to clinical trials after preclinical studies showed satisfactory brain penetration, target engagement, and a significant reduction of Aβ plaques in transgenic mice brains.[6,33] The first Phase 1 trial began in 2011 (study 101, NCT01397539), aiming to evaluate the safety, tolerability, and pharmacokinetics (PK) of an ascending dose of aducanumab (0.3 mg/kg to 60 mg/kg). The study showed a reasonable safety profile and linear PK at doses ≤ 30mg/kg.[34] In 2012, a phase 1b randomized trial, denominated PRIME (study 103, NCT01677572), started with mild cognitive impairment (MCI) and mild AD patients who had brain Aβ plaques confirmed by positron emission tomography (PET) imaging. Participants received monthly intravenous infusions of aducanumab at doses 1, 3, 6, and 10 mg/Kg to examine the safety, tolerability, PK, and pharmacodynamics. Biogen also performed an exploratory clinical evaluation in PRIME. Results showed that ARIA was the most common side effect, increasing with dose and ApoE4 genotype (a genetic risk
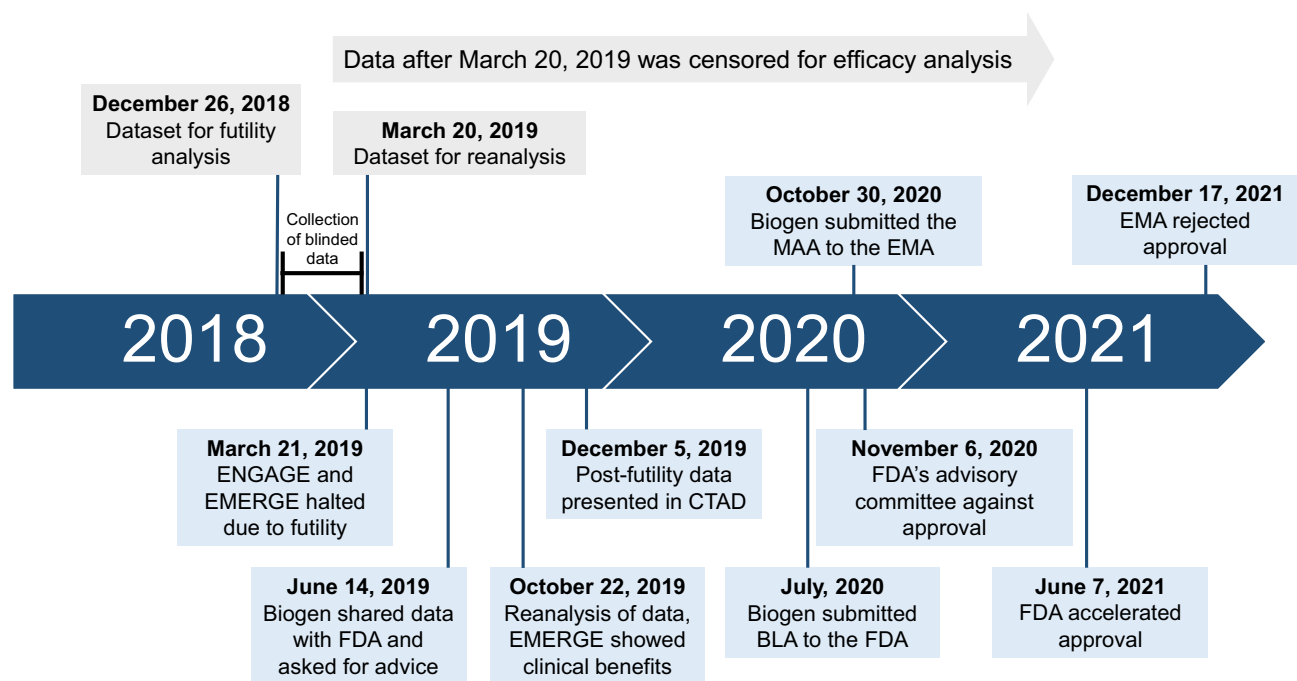
Figure 1 Aducanumab timeline since futility analysis until regulatory agencies decisions.
Abbreviations: BLA, Biologics License Application; EMA, European Medicines Agency; FDA, US Food and Drug Administration; MAA, Marketing Authorization Application.

factor for AD), and revealed a significant time and dose-dependent reduction of brain Aβ plaques. In addition, researchers reported a dose-dependent slowing of cognitive deterioration, measured by two dementia rating scales.[6] The PRIME was the first trial to demonstrate a possible correlation between the reduction of brain Aβ and clinical benefits by an anti-Aβ antibody (proof of concept).[19]

These promising results prompted the start of phase 3 trials under a special protocol assessment with the FDA.[19] Therefore, in 2015, Biogen initiated simultaneously two identical, large, global, double-blind, randomized, placebo-controlled, phase 3 studies: ENGAGE (study 301, NCT02477800) and EMERGE (study 302, NCT02484547). The studies aimed to assess efficacy and safety in MCI and mild AD patients with a positive amyloid PET scan for 18 months. The two studies enrolled 3285 participants from 20 countries and were supposed to run until 2022.[19,35]

However, on March 21, 2019, Biogen announced the early termination of both phase 3 trials (Figure 1). The decision was made after an interim analysis had demonstrated that EMERGE and ENGAGE were unlikely to reach their primary efficacy endpoint, the slowing of cognitive decline.[36] This futility analysis was performed using pooled data from both studies, collected up to December 26, 2018 (when approximately 50% of participants completed week 78 of the trials). Though, if the trials had been independently assessed (using non-pooled data), EMERGE would not have met the futility criteria.[19,35,37] Given this observation, the sponsor decided to collect three additional months of blinded data, between the date cutoff of futility analysis and the public futility announcement (Figure 1). The reanalysis of this larger dataset showed that the high-dose arm in EMERGE met the primary endpoint, while ENGAGE was a failed study. In June 2019, Biogen shared this data with the FDA asking for advice on the validity of the results and their interpretation, given the premature discontinuation. After four months of analysis, the FDA considered that data are interpretable and reliable for further conclusions, but efficacy data collected after March 20, 2019, should be censored.[19]

On October 22, 2019, Biogen formally announced that aducanumab showed a statistically significant clinical benefit in EMERGE, reaching primary and secondary endpoints. In contrast, the ENGAGE trial did not meet any of the endpoints. Despite that, Biogen's researchers considered that ENGAGE is not a negative study, as a subset of patients who received sufficient exposure to the high-dose of aducanumab had similar benefits to those reported in EMERGE (trials data will be explored later in this article).[38] Based on these results, and with PRIME trial providing additional

evidence of effectiveness, the FDA considered that a marketing application for aducanumab was reasonable. Thus, Biogen submitted a Biologics License Application (BLA) to the FDA in July 2020 (Figure 1).[19]

In short, the BLA of aducanumab was based on data from 3 trials. EMERGE is a robust positive trial that has proven a cognitive decline reduction. ENGAGE is a partially discordant study whose post hoc analysis supports the EMERGE results. PRIME is a phase Ib trial whose clinical exploratory assessment demonstrated a positive outcome. The partially divergent results and the absence of further studies raised a considerable debate about the decisions of regulatory agencies.

FDA Decision

On November 6, 2020, the Peripheral and Central Nervous System (PCNS) Drugs Advisory Committee met to evaluate the clinical data of aducanumab. None of the members voted in favor of aducanumab's approval (10 against, 1 abstention). They considered that the results of the studies were conflicting, and the data presented did not show sufficient evidence of clinical efficacy.[19,39] Contrary to the independent committee decision, the FDA granted accelerated approval to aducanumab on June 7, 2021, leading to the resignation of three members of the PCNS committee.[20,40] The accelerated approval pathway allows patients to have early access to drugs that target a serious disease and which provide a meaningful improvement over current treatments. This approval is based on a surrogate endpoint that is thought to predict clinical benefit, and not on clinical outcomes. In this case, the FDA believes that the reduction of brain Aβ plaques is a biomarker reasonably likely to predict the slowing of cognitive decline. Furthermore, the accelerated approval program requires a post-approval trial to confirm clinical benefits. If the trial fails to show clinical benefits or the risks outweigh the benefits, aducanumab approval will be withdrawn.[5,41]

EMA and PMDA Decisions

In Europe, aducanumab was under review at the EMA since October 2020 (Figure 1).[14,42] On December 17, 2021, the EMA's Committee for Medicinal Products for Human Use recommended the rejection of the marketing application for Aduhelm™.[22,43,44] According to the performed studies, EMA experts considered that this drug did not show a clear signal of efficacy nor a satisfactory safety profile to treat patients in the early stage of AD.[22] In contrast to the FDA, they considered that reduction of brain Aβ aggregates is not an acceptable biomarker to predict clinical benefit. At the time of press, Biogen is appealing against EMA's decision.[23,44] Shortly after the EMA's decision, the Japanese Medicines agency also denied the approval of aducanumab. For the PMDA, trials results are inconclusive and they require additional data before considering Aduhelm™ approval.[23,24]

Ongoing Studies and Confirmatory Trial

Currently, Biogen is running two clinical studies: EMBARK and ICARE-AD. The EMBARK (NCT04241068) is a phase 3b, open-label, extension study enrolling patients that previously participated in aducanumab studies (PRIME, EVOLVE, ENGAGE and EMERGE). This study intends to assess the safety and efficacy of aducanumab after prolonged treatment interruption.[45,46] On the other hand, ICARE-AD (NCT05097131) is an observational study designed after aducanumab's approval. It is a prospective cohort aiming to collect safety and efficacy data in clinical practice (Phase 4).[47,48] Moreover, Biogen is still designing the FDA's required phase 4 confirmatory study, a new global, placebo-controlled clinical trial named ENVISION. The company intends to start recruiting patients in May 2022, and the study should be completed in 2026.[49,50]

Data from ENGAGE and EMERGE Clinical Trials

To date, full clinical trials data have not been published in a peer-reviewed journal. The results presented below were obtained from Biogen's presentation at the Alzheimer's Disease Conference (CTAD) in December 2019 and from the combined FDA and Biogen briefing document that emerged from the PCNS Drugs Advisory Committee meeting.[19,32,35] Therefore, we cannot exclude any potential bias introduced by the sponsor.

The ENGAGE (1647 patients) and EMERGE (1638 patients) were two phase 3 trials identically designed to assess aducanumab's safety and efficacy in MCI and mild AD patients. Participants were randomized 1:1:1 in placebo and two-

dose regimens of aducanumab: low-dose (3 and 6 mg/kg for Apolipoprotein E (ApoE) ε4 carriers and non-carriers, respectively) and high-dose (6 and 10 mg/kg for ApoE ε4 carriers and non-carriers, respectively). After protocol version 4 (PV4), the high-dose in ApoE ε4 carriers increased to 10 mg/kg.[19,39]

Efficacy

The main objective of these studies was to assess the efficacy of aducanumab in reducing cognitive decline. Biogen used four recognized clinical efficacy scales to measure it. The primary endpoint was the change in Clinical Dementia Rating-Sum of Boxes (CDR-SB) from baseline to week 78. Secondary objectives were to evaluate the changes in Mini-Mental State Examination (MMSE), Alzheimer's Disease Assessment Scale-Cognitive Subscale (13-item version) (ADAS-Cog 13), and Alzheimer's Disease Cooperative Study-Activities of Daily Living Inventory-Mild Cognitive Impairment version (ADCS-ADL-MCI). In addition, sub-studies were conducted to analyze the changes in amyloid PET, tau PET, and in CSF (cerebrospinal fluid) biomarkers such as phosphorylated tau (p-tau), total tau (t-tau), and 42-amino acid form of amyloid β (Aβ$_{42}$).[19]

The efficacy data are presented in Table 1. Both studies showed a reduction in brain Aβ, measured by PET, in all treatment groups compared to placebo ($p<0.0001$). This reduction was dose-dependent. However, only the high-dose arm of EMERGE showed a statistically significant benefit on CDR-SB ($p<0.05$) and all the secondary outcomes: MMSE, ADAS-Cog 13 and ADCS-ADL-MCI ($p<0.05$). ENGAGE did not demonstrate significant differences between the patients treated with aducanumab and placebo on primary and secondary efficacy outcomes. Moreover, the results of the low-dose arm were numerically better than the high-dose (Table 1).

Besides amyloid PET, the other sub-studies (tau PET, p-tau, t-tau, and Aβ$_{42}$) were performed on a small number of subjects, with less than 10% of the studies participants undergoing these analyses.[37] Tau PET was evaluated using combined data from ENGAGE and EMERGE trials, comprising only 37 patients. As presented in Table 2, aducanumab produced

Table 1 Efficacy and Biomarker (Amyloid PET) Final Data at Week 78 in ENGAGE and EMERGE Studies

	ENGAGE (Study 301)			EMERGE (Study 302)		
	Placebo Decline **N=545**	**Difference vs Placebo (%) p-value**		**Placebo Decline** **N=548**	**Difference vs Placebo (%) p-value**	
		Low-Dose ADU (3 or 6 mg/kg) N=547	**High-Dose ADU (6 or 10 mg/kg)[a] N=555**		**Low-Dose ADU (3 or 6 mg/kg) N=543**	**High-Dose ADU (6 or 10 mg/kg)[a] N=547**
CDR-SB	n=333 1.56	n=331 -0.18 (−12%) p=0.2250	n=295 0.03 (2%) p=0.8330	n=288 1.74	n=290 −0.26 (−15%) p=0.0901	n=299 −0.39 (−22%) **p=0.0120**
MMSE	n=332 −3.5	n=334 0.2 (−6%) p=0.4795	n=297 −0.1 (3%) p=0.8106	n=288 −3.3	n=293 −0.1 (3%) p=0.7578	n=299 0.6 (−18%) **p=0.0493**
ADAS-Cog 13	n=331 5.140	n=332 −0.583 (−11%) p=0.2536	n=294 −0.588 (−11%) p=0.2578	n=287 5.162	n=289 -0.701 (−14%) p=0.1962	n=293 −1.400 (−27%) **p=0.0097**
ADCS-ADL -MCI	n=331 −3.8	n=330 0.7 (−18%) p=0.1225	n=298 0.7 (−18%) p=0.1506	n=283 -4.3	n=286 0.7 (−16%) p=0.1515	n=295 1.7 (−40%) **p=0.0006**
Amyloid PET	n=104 −0.005	n=116 −0.163 **p<0.0001**	n=97 −0.233 **p<0.0001**	n=74 0.019	n=79 −0.184 **p<0.0001**	n=87 −0.291 **p<0.0001**

Notes: Negative percentage means less AD progression in the treated arm. Bold indicator means a statistically significant difference (p<0.05). [a]After protocol version 4, high-dose was titrated to 10 mg/kg for all patients of this arm (ApoE ε4 carriers and non-carriers). Data from Biogen.[32,35]
Abbreviations: ADAS-Cog 13, Alzheimer's Disease Assessment Scale-Cognitive Subscale (13 items); ADCS-ADL-MCI, Alzheimer's Disease Cooperative Study-Activities of Daily Living Inventory-Mild Cognitive Impairment version; ADU, Aducanumab; CDR-SB, Clinical Dementia Rating-Sum of Boxes; MMSE, Mini-Mental State Examination; n, number of randomized and dosed subjects with week 78 endpoint assessment; N, number of participants enrolled; PET, Positron Emission Tomography.

Table 2 Changes from Baseline in Tau PET

Tau PET Composite Region	Placebo Change n=12	Difference vs Placebo p-value	
		Low-Dose ADU n=14	High-Dose ADU n=11
Frontal	0.090	−0.049 p=0.0876	−0.073 **p=0.0212**
Medial Temporal	0.082	−0.115 **p=0.0012**	−0.132 **p=0.0005**
Temporal	0.082	−0.065 p=0.1174	−0.096 **p=0.0304**

Notes: Bold indicator means a statistically significant difference (p<0.05). Data pooled from EMERGE and ENGAGE.[19,35]
Abbreviations: ADU, Aducanumab; n, number of subjects enrolled in Tau PET sub-study; PET, Positron Emission Tomography.

a dose-related reduction in brain tau levels in frontal (p<0.05), medial temporal (p<0.001), and temporal (p<0.05) composite brain regions. The medial temporal region experienced the highest reduction of tau levels, with statistical significance in both low and high-dose administration of aducanumab (p=0.0012 and p=0.0005, respectively). The cingulate, parietal, and occipital composites did not show a significant difference relative to placebo, but numeric data were not provided.[19,51] In addition, the changes in CSF biomarkers (p-tau, t-tau, $A\beta_{1-42}$) were not presented in sufficient detail for both trials. Despite that, available data demonstrated that aducanumab produced a significant dose-dependent reduction of CSF p-tau and t-tau in EMERGE trial. In ENGAGE, p-tau and t-tau also decreased in the aducanumab-treated patients, but the low-dose arm showed a higher reduction than the high-dose arm.[19,35,37] Finally, the $A\beta_{42}$ analysis is unavailable for ENGAGE, but in EMERGE, aducanumab increased the CSF $A\beta_{42}$ levels in a dose-response relationship.[19]

Safety

In terms of safety, ARIA was the most common adverse event in ENGAGE and EMERGE. ARIAs are abnormal findings detected in brain magnetic resonance imaging (MRI) and can present as brain edema or sulcal effusions (ARIA-E) and as intracerebral hemorrhage often accompanied by superficial hemosiderin deposits (ARIA-H).[52] Although the mechanism leading to ARIA remains not fully understood, studies suggest that Aβ clearance causes damage to vessel walls which increases the cerebrovascular permeability and the risk of hemorrhage.[52,53] ARIA has been associated with anti-Aβ antibodies therapies and was reported in the phase 1b trial of aducanumab (PRIME).[6,52,54–56]

Salloway et al published the combined safety data from the ENGAGE and EMERGE trials in December 2021.[21] However, we presented the ARIA incidence for each study independently in Table 3. In general, around 40% of the patients taking the aducanumab high-dose developed ARIA (ARIA-E or ARIA-H), compared to 10% on placebo (Table 3). Although most of the patients were asymptomatic (ARIA was detected only in MRI), some patients experienced symptoms such as headache, dizziness, visual disturbance, and nausea.[21,35] ARIA-E was the most common adverse event, occurring in approximately 35% of the patients in the high-dose group (35.7% and 34.4% for ENGAGE and EMERGE, respectively) compared with 3% in the placebo group (3% and 2.2% for ENGAGE and EMERGE, respectively) (Table 3). The ARIA-E incidence increased with aducanumab dose and was higher among ApoE4 carriers than in non-carriers, in the aducanumab-treated patients (Table 3).

Moreover, brain microhemorrhages were the most common type of ARIA-H in both trials (17.7% and 18.9% in the high-dose group of ENGAGE and EMERGE, respectively) (Table 3). According to Salloway et al's analysis, ARIA-H are more frequent in patients who also had ARIA-E (approximately 40% of ARIA-E patients had ARIA-H). Finally, despite the high incidence, ARIA episodes typically resolved in 4–16 weeks, and less than 1% of patients treated with aducanumab experienced severe ARIA symptoms.[21]

Table 3 Summary of ARIA Incidence in ENGAGE and EMERGE Studies, in the Placebo-Controlled Period

	ENGAGE (Study 301)			EMERGE (Study 302)		
	Placebo N=533	Low-Dose ADU N=544	High-Dose ADU N=554	Placebo N=544	Low-Dose ADU N=537	High-Dose ADU N=541
ARIA (either E or H) (%)	9.8	30.7	40.3	10.3	32.8	41.2
Asymptomatic	94.2	83.2	70.9	94.6	78.4	80.3
Symptomatic	5.8	16.8	29.1	5.4	21.6	19.7
ARIA-E (%)	3.0	25.6	35.7	2.2	26.1	34.4
ApoE ε4 carriers	2.4	28.7	41.8	1.9	29.8	42.5
ApoE ε4 non-carriers	4.3	17.5	22.7	2.9	18.1	17.9
ARIA-H, microhemorrhage (%)	5.8	15.6	17.7	7.0	16.4	18.9
ARIA-H, superficial siderosis, (%)	1.9	8.8	15.5	2.6	9.3	13.5
ARIA-H, macrohemorrhage (%)	0.8	0	0.5	0	0.2	0.6

Note: Data from Biogen.[35]
Abbreviations: ApoE, Apolipoprotein E; ADU, Aducanumab; ARIA, Amyloid Related Imaging Abnormalities; ARIA-E, Amyloid Related Imaging Abnormalities due to Edema/Effusion; ARIA-H, Amyloid Related Imaging Abnormalities due to Microhemorrhage, Superficial Siderosis or Macrohemorrhage; N, Patients with at least one post-baseline magnetic resonance imaging.

Discordant Results and Post Hoc Analysis

The divergent outcomes of the trials are the main controversy over aducanumab approval. Investigators consider that two identically designed studies, not fully completed, whose results directly contradict each other cannot prove the efficacy of aducanumab.

Biogen researchers performed a post hoc analysis of data to understand the differences between the ENGAGE and EMERGE trials. They found two possible explanations for these differences: duration of exposure to high-dose aducanumab and imbalance of rapid disease progressors. Firstly, exposure to a high dose of aducanumab is seen as the critical variable for the different outcomes. In total, 29% of the patients in EMERGE received the full possible 14 doses of 10 mg/kg of aducanumab compared to 22% of the patients in ENGAGE.[19,35,37] Several factors contributed to this exposure discrepancy, such as the beginning of the trials, the timing of implementation of PV4 (allowed ApoE ε4 carriers to receive 10 mg/kg), and the timing of futility analysis. Moreover, Biogen presented a subset of data limited to patients exposed to PV4 who received 14 infusions of 10 mg/kg of aducanumab (Table 4). In this analysis, ENGAGE subset of patients showed a reduction in cognitive decline, measured by CDR-SB, similar to EMERGE (−0.48 and −0.53 for the high-dose arm of ENGAGE and EMERGE, respectively) (Table 4). The second factor that explains the difference between the trials was the higher number of rapid progression patients in the high dose arm of ENGAGE compared to EMERGE (9 and 5 patients, respectively). Exploration showed that excluding the rapid progressors, the CDR-SB changes from 0.03 (2%), see Table 1, to −0.09 (−6%) in the high-dose of ENGAGE.[19,32] The other groups were not affected by rapid progressors.

Although this examination appears to confirm that ENGAGE trial supports the positive results of EMERGE, post-hoc analyzes do not have the same predictive power as the primary assessments due to the possible introduction of bias. Knopman et al mentioned in their review that although plausible, post hoc explanations are insufficient to justify a claim of efficacy for aducanumab.[37] The same author states that the variance in placebo decline is an alternative explanation for the different results of the trials. The placebo group declined 1.56 points for CDR-SB in ENGAGE, while in EMERGE,

Table 4 Changes in CDR-SB in Intention to Treat (ITT) Population Compared to Post-Protocol Version 4 (PV4) Population Who Received 14 High-Dose Aducanumab Treatments for ENGAGE and EMERGE Studies at Week 78

	ENGAGE (Study 301)			EMERGE (Study 302)		
	Placebo Decline	Difference vs Placebo (%)		Placebo Decline	Difference vs Placebo (%)	
		Low-Dose ADU	High-Dose ADU		Low-Dose AD	High-Dose ADU
ITT						
CDR-SB	n=333 1.56	n=331 −0.18 (−12%)	n=295 0.03 (2%)	n=288 1.74	n=290 −0.26 (−15%)	n=299 −0.39 (−22%)
PV4						
CDR-SB	n=247 1.79	n=261 −0.35 (−20%)	n=282 −0.48 (−27%)	n=304 1.76	n=295 −0.42 (−24%)	n=288 −0.53 (−30%)

Note: Data from Biogen.[35]
Abbreviations: ADU, Aducanumab; CDR-SB, Clinical Dementia Rating-Sum of Boxes; ITT, intention to treat population; n, number of subjects with week 78 endpoint assessment; PV4, Protocol Version 4.

the decline was 1.74 points (Table 1). The higher placebo decline in EMERGE could explain the statistically significant clinical benefit in the high-dose arm.[37] Identically, the higher placebo decline in the PV4 patient's subgroup compared to the original intention to treat (ITT) population in ENGAGE (1.79 vs 1.56 points in CDR-SB) is a potential reason for the better outcomes and not necessarily the exposure to high-dose of aducanumab (Table 4).[37] However, we should note that the cognitive performance of placebo groups is not consistent, as it differs from the other efficacy endpoints. In ADAS-Cog 13 evaluation, placebo decline was similar in both trials, but in MMSE the decline was higher in ENGAGE than in EMERGE (Table 1).[19]

Furthermore, the duration of exposure to high-dose aducanumab does not explain why the low-dose arm in ENGAGE was numerically better than the high-dose, despite none of the participants being exposed to 10 mg/kg of aducanumab (Table 1). In fact, the high-dose arm in ENGAGE was worse than the placebo in CDR-SB and MMSE measures (p=0.8330 and p=0.8106, respectively) (Table 1). Further, Knopman et al pointed out that the significantly better results in the low-dose arms of PV4 patient's subset appear to contradict the argument that the exposure to 10 mg/kg dose of aducanumab is the main responsible for clinical efficacy (Table 4).[37]

Finally, researchers have raised some questions about ARIA management. Although Biogen mentioned that bias due to ARIA is not apparent, some authors still consider that the sporadic unblinding due to ARIA episodes management could have impacted the results. The incidence of ARIA was higher in aducanumab-treated patients, and all the four efficacy outcomes may be subject to bias when drug assignment is known.[19,32,57]

Biomarkers Analysis

The results showed a clear target engagement of aducanumab, with a significant dose-dependent reduction of Aβ in PET. However, there is a lack of correlation between Aβ PET changes and cognitive changes, measured by CDR-SB, for high-dose patients.[19] This observation raises doubts about the biomarker-based approval of aducanumab by the FDA. Similarly, the tau biomarkers also decreased with aducanumab treatment, but the correlation between tau changes and CDR-SB is not significant in the high dose.[19] Though, the small sample size of tau substudies (p-tau, t-tau, and tau PET) limits the conclusions due to possible statistical noise.

Bearing this last point in mind, Biogen asked independent researchers to analyze stored plasma samples from 1815 ENGAGE and EMERGE trials participants. Data presented at the 2021 CTAD conference showed that aducanumab produced a time and dose-dependent reduction of plasma p-tau. Moreover, the results demonstrated that plasma p-tau reduction had a statistically significant correlation with less clinical decline on all four efficacy outcomes measures and with the lowering of Aβ plaques.[58]

In short, aducanumab appears to have an effect on both main pathological features of AD (Aβ and tau protein). Further, this analysis showed that p-tau has the potential to be a better surrogate endpoint for cognition than Aβ plaques.

Controversy

After aducanumab's approval, several experts manifested disagreement with the decision of the FDA.[11–13] In this section, we will explore the controversial points of aducanumab.

Firstly, as mentioned above, the conflicting results of phase 3 trials are the main core of the controversy. The data available and the post hoc analysis do not provide sufficient evidence to support the clinical efficacy of aducanumab. The FDA should have required a third phase 3 trial with a high-dose of aducanumab before approval.[37,59] Secondly, there is no evidence that Aβ reduction correlates with clinical benefits, so the majority of experts consider that Aβ plaques are not a valid surrogate endpoint.[10,60] Moreover, recent studies showed that tau accumulation correlates better with cognitive impairment than Aβ.[61,62] Thirdly, the close collaboration between the FDA and the sponsor could have impacted the objectivity of the FDA's decision.[63,64] Furthermore, the AD's advocacy groups exerted much pressure on the FDA, defending that a marginal benefit of aducanumab would be significant to patients and caregivers.[65] Fourthly, the FDA's decision passes to physicians the unfair role of removing false hopes from patients.[59] Fifthly, aducanumab approval could prejudice scientific development, leading pharmaceutical companies to abandon other targets associated with AD, redirecting their efforts towards amyloid pathology and using an unproven biomarker to obtain approval. Currently, two new monoclonal anti-Aβ antibodies are under review by the FDA: lecanemab (Eisai/Biogen) and donanemab (Eli Lilly's). Gantenerumab also gained new interest after aducanumab approval.[39,65]

In addition, there is also a substantial debate about the cost-effectiveness and the safety of aducanumab. Initially, aducanumab had an annual cost of US$ 56,000 per person, but Biogen reduced the price to half at the beginning of 2022. Despite that, the value remains much higher than the $2500-$8300 predicted for aducanumab to be cost-effective.[11,66–68] Further, given the ARIA high incidence under trials conditions (40% high dose aducanumab vs 10% in placebo), there are some concerns about whether the benefits outweigh the risks in the clinical practice. Importantly, monitoring the ARIA with MRI scans will increase the cost of treatment and the complexity of infrastructures needed.[39]

Finally, there was controversy over the FDA prescribing label for aducanumab because it was initially approved for anyone with AD, despite the trials only enrolled MCI and mild AD patients.[13] Only after a month, the FDA narrowed the indication to MCI and mild AD.[12,51] Moreover, the prescribing information does not require a positive amyloid biomarker (amyloid PET or CSF biomarkers) to confirm the diagnosis of AD.[39,51] This fact appears to be contradictory, once all participants of ENGAGE and EMERGE had a positive amyloid PET and being Aβ plaques the aducanumab target. Therefore, an expert panel published a use recommendation for aducanumab to cover these critical issues and guide clinicians. We explore it in the next section.[69]

Use Recommendations of Aducanumab

The Expert Panel, headed by Cummings, recommends using aducanumab in patients with a diagnosis of MCI and mild AD. In addition, they consider mandatory a positive amyloid PET or CSF biomarkers consistent with AD and a score ≥ 21 in MMSE (or equivalent cognitive test) to initiate treatment. ApoE genotype screening is optional, despite the high risk of ARIA in ApoE4 carriers.[69]

The panel also requires aducanumab titration to the target dose of 10 mg/kg over 6 months, and this dose is continued for the future (Figure 2). Aducanumab is administered as an intravenous infusion over 45–60 minutes every month, and the titration aims to minimize the risk of ARIA. To monitor ARIA, they recommend a brain MRI one year before the first administration of aducanumab and prior to the 5th (before initiating 6 mg/kg), 7th (before the target dose of 10 mg/kg), and the 12th infusions (after 6 doses of 10 mg/kg). An additional MRI should be considered before the 10th infusion, given the high incidence of ARIA in 10 mg/kg dose (Figure 2). Patients with ARIA symptoms or moderate to severe asymptomatic ARIA should suspend or discontinue the treatment. Finally, the expert panel does not recommend aducanumab treatment in preclinical and moderate to severe AD patients because no data is available for these AD stages.[69]
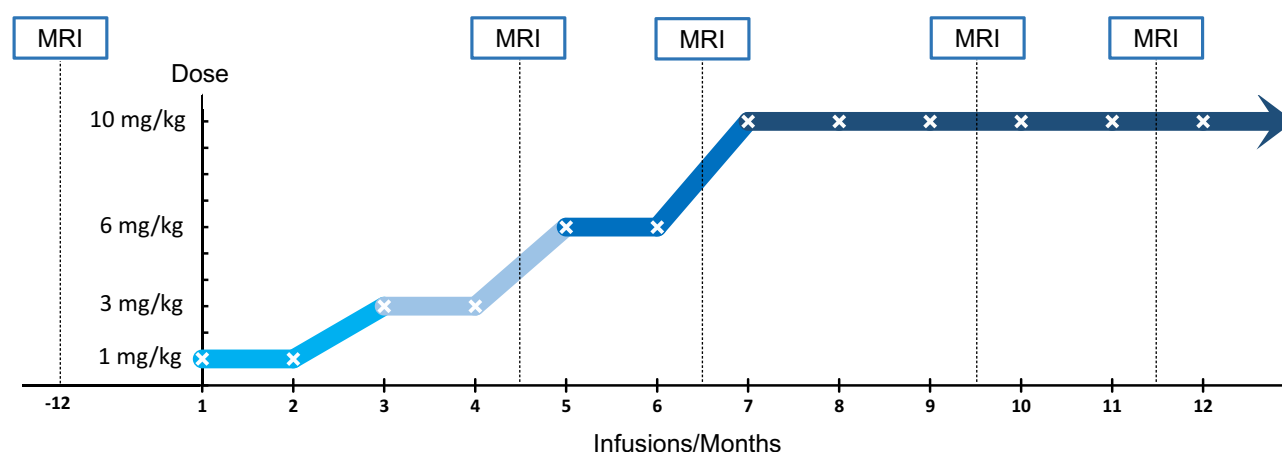
Figure 2 Dose titration of aducanumab from 1 mg/kg to 10 mg/kg and magnetic resonance imaging monitoring.
Abbreviations: MRI, Magnetic Resonance Imaging.

Challenges and Opportunities

Despite controversies, aducanumab is a new drug for a disease that significantly impacts individuals and society. Its approval generated challenges and opportunities for the management of AD.

The high cost of aducanumab is probably the most challenging point surrounding its approval, especially because aducanumab treatment is not time-limited. Its questionable efficacy and the initial price of US\$ 56,000 led many insurances and hospitals to refuse to cover the cost of the treatment. Consequently, few patients had access to Aduhelm™ in the first six months, with disappointing sales for Biogen. After the rejection of EMA, Biogen announces the reduction of the price to \$28,200 at the beginning of 2022, expecting to improve patient's access to aducanumab through an increase in insurance coverage.[67]

However, on April 7, 2022, the Centers for Medicare and Medicaid Services (CMS) restricted aducanumab coverage only to clinical trials (randomized controlled trials).[70,71] There has been a considerable debate since the announcement that CMS planned to limit Aduhelm™ coverage.[72] The CMS decision includes the whole class of anti-Aβ antibodies, which also affect lecanemab, donanemab, and gantenerumab.[73,74] Moreover, this decision could also interfere with private insurance coverage because most follow the CMS's orientations.[74] Furthermore, Biogen had to adapt its confirmatory study (ENVISION) to be covered by the CMS.[50]

In addition, aducanumab approval created challenges for current and future AD clinical trials. Firstly, patients will want to drop out of investigational drugs trials for the aducanumab.[39] Secondly, it could be challenging to recruit and keep patients in placebo-controlled trials.[12,13]

Moving to the opportunities, aducanumab's effect on downstream tau pathology could finally empower the combination therapies approach (anti-tau and anti-amyloid drugs). Given the complexity of AD pathology, combined therapy is gaining strength in the scientific community. Having one anti-Aβ immunotherapy approved, with the demonstrated effect of tau pathology, could open the door for clinical trials targeting more than one toxic protein.[75]

Further Implications of Aducanumab Approval

Aducanumab approval will have a major impact on AD therapy. The FDA's decision can redirect the investigation efforts towards the amyloid hypothesis, a therapeutic approach that would be practically "dead" in the face of aducanumab's failure.

Furthermore, this accelerated approval will also have significant implications in other therapeutic areas, namely in oncology which have a high proportion of drugs approved by the accelerated pathway. Lythgoe et al published a critical paper covering this subject.[76] The authors stated that the FDA's decision suggests that any biomarker can be used as a surrogate endpoint to submit for accelerated approval, regardless of whether or not it is validated. Additionally, aducanumab's approval showed that despite negative clinical trials or negative advisory committee opinions, drugs can receive

accelerated approvals. Thus, an exponential increase in accelerated approvals of anti-cancer drugs is expected in the coming years, and some of them may have dubious efficacy. Finally, the authors indicated that the large time given to Biogen to complete the confirmatory trial (9 years) could set a precedent for companies to delay the completion of this trial.[76] As a result, some experts are now questioning the utility of FDA´s accelerated approvals, showing concerns about its increasing frequency, and suggesting reform of this pathway.[77]

Conclusion

Aducanumab has been the most promising drug for AD of the last decade. However, the divergent results between ENGAGE and EMERGE and its post hoc analysis did not show sufficient evidence of clinical benefit. In addition, there is no reliable evidence that correlates Aβ plaques reduction with clinical efficacy to support the FDA approval. Some authors mention that a third randomized, placebo-controlled, phase 3 clinical trial is necessary to prove aducanumab efficacy.[37] Moreover, at best, aducanumab has a modest benefit in AD, which coupled with its high cost and adverse events (ARIA) raise questions about whether the benefits outweigh the risk and the cost burden to healthcare systems. Therefore, the recent decision of CMS has been seen as a correction to the original approval of the FDA by many experts, and we share that vision.[73,74] In this article, we tried to give a balanced and objective perspective on the data and the trajectory of aducanumab. However, in our opinion, the EMA and the PMDA took the right decision by refusing to approve aducanumab.

Despite the controversy, it is clear that aducanumab reduces significantly the Aβ in the brain, one of AD's hallmarks. Further, the results also showed that aducanumab acts on the second AD's hallmark, decreasing tau brain levels. This observation could become a turning-point for the approach therapy to AD. Researchers are concluding that both Aβ and tau protein has a major role in the neurodegeneration process and they interfere with each other.[78] Thus, a combination therapy targeting the accumulation of Aβ aggregates (upstream pathology) and the intracellular tau accumulation (downstream pathology) have the potential to change the natural progress of AD.[75] The combination therapy is now a necessity.[79]

In conclusion, we hope that aducanumab approval does not redirect the focus of research only to Aβ immunotherapies. Targeting AD in multiple pathways could be the most effective way to have a truly disease-modifying therapy for this epidemic of our century.

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Disclosure

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