Two Randomized Phase 3 Studies of Aducanumab in Early Alzheimer's Disease[1]

EMERGE & ENGAGE Trial Summary (2022)

SUMMARY

In patients with mild cognitive impairment (MCI) due to Alzheimer's disease (AD) with amyloid pathology, **aducanumab** had *inconsistent* evidence to show a statistical and clinical improvement in the condition. There was however, a statistically significant reduction shown in amyloid PET scans, however this has not shown to impact clinical outcomes in AD. Furthermore, there were high rates of adverse effects, which are detailed below.

Note: The **EMERGE** and **ENGAGE** trials were identically designed trials which were terminated early due to the outcome of a futility analysis. Futility analyses are included in clinical studies to prevent participants from receiving ineffective treatments.

Bottom Line:

- Inconsistent results between these two identical trials with numerous limitations. More clinically meaningful evidence required before this would be considered a feasible intervention for mild cognitive impairment in AD.

BACKGROUND

- Alzheimer's Disease is a progressive neurological disorder, thought to be caused by beta-amyloid plaques and neurofibrillary tangles.[1]
- Beta-amyloid plaques and slowing their formation has been the target of drug therapy research for years.[1]

EMERGE & ENGAGE METHODS (SEE ORIGINAL ARTICLE/SUPPLEMENT FOR FULL CRITERIA)

DESIGN: Two identically designed trials: both randomized, double blind, placebo-controlled, multi-centre, phase 3 studies of aducanumab in patients with early Alzheimer's Disease.

- The randomization was stratified by site and apolipoprotein E (ApoE) ε4 carrier status (1:1:1).
- Pharmacy staff were unblinded and managed study treatment receipt, dispensing, and preparation. Treatment assignments were not shared with the participants, their families, or any member of the blinded study team.
- Used modified intention-to-treat to assess primary outcome (all patients who had received at least one dose).
- **Funding**: The study was sponsored by Biogen (aducanumab manufacturer). Biogen designed and conducted the study, as well as collection, analysis, and interpretation of the data.
- **Enrollment**: **ENGAGE** enrolled starting Aug 2015, **EMERGE** enrolled starting Sept 2015. Both stopped recruitment July 2018.
  - Two protocol amendments were implemented that aimed to enable more participants in the high-dose arms to achieve the target dose of 10 mg/kg:
    1) Participants who suspended dosing due to amyloid-related imaging abnormalities (ARIA) could, after resolution of ARIA, resume dosing at the same dose and continue titration to the target dose (rather than having the dose reduced).
    2) To maximize the dose-dependent effect of aducanumab, the target dose for ApoE ε4+ carriers in the high-dose regimen was increased from 6 to 10 mg/kg (approved March 2017).
  - The number of patients enrolled in **ENGAGE** was ahead of the **EMERGE** (by about 200 patients), therefore more patients in **EMERGE** were affected by the protocol changes (e.g. to go to a higher dose earlier in the trial) than those in **ENGAGE**.

INTERVENTION: Aducanumab low dose (3 or 6 mg/kg target dose) vs aducanumab high dose (6 or 10mg/kg target dose; changed to 10 mg/kg target dose after protocol amendment) vs placebo via IV infusion once every 4 weeks over 76 wk.

POPULATION:

- **INCLUSION**: Patients aged 50 to 85 years (mean age 70yr) who met clinical criteria for MCI due to AD or mild AD dementia, with amyloid pathology confirmed by visual assessment of amyloid positron emission tomography, MMSE score of 24-30, & CDR-SB=0.5.
- **EXCLUSIONS**: MRI was used to exclude patients with confounding pathologies (acute hemorrhage, microhemorrhage, infarction, superficial siderosis, or history of white matter disease), negative amyloid PET scan, not meeting diagnostic criteria, uncontrolled diabetes, & other AD meds not stable for ≥4wk.

POPULATION: at baseline: 6757 people screened with 1643 people randomized (24%) in **EMERGE**; 6173 people screened with 1653 people randomized (27%) in **ENGAGE**

- Average characteristics for both trials: age = ~70 years old, ~50% female, 75%-80% white ethnicity, MMSE score of ~26
- ~67% were ApoE ε4+ carriers (meaning they were moved to the high dose treatment part-way through because of the protocol amendment)

OUTCOMES – over 76 weeks:

- **Primary:** change from baseline to week 78 (2wk follow up) on the Clinical Dementia Rating Sum of Boxes (CDR-SB), an integrated scale that assesses both function and cognition.
  - The proposed minimally clinically important difference (MCID) on the CDR-SB scale is 1 point.[2]
- **Secondary**: Mini-Mental Status Exam (MMSE), Alzheimer's Disease Assessment Scale–Cognitive Subscale–13 items (ADAS-Cog13), Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory–Mild Cognitive Impairment (ADCS-ADL-MCI).
- A subset of patients (n=488 in **EMERGE**; n=585 in **ENGAGE**) were also assessed for amyloid PET changes from baseline to week 26 & 78
  - A substantial decrease in amyloid PET % from baseline was seen with both high and low doses, relative to placebo which stayed relatively stable.

TRIAL STOPPED EARLY: Based on analysis of results from a pre-specified futility analysis of interim data, after which ~50% of participants had completed week 78 (**ENGAGE** 57%, **EMERGE** 49%), there appeared to be no clinical benefit for the intervention. The independent data monitoring committee recommended to terminate the study. Excluded data collected after March 2019. Final data set included 65.2% of the data observations planned.

RESULTS

follow up over 18 months (1.5yr)

TABLE 1: EFFICACY & SAFETY

Clinical Endpoints	ENGAGE					EMERGE				
	Placebo n=545	Aducanumab low dose n=547	Absolute Difference (95% CI)	Aducanumab high dose n=555	Absolute Difference (95% CI)	Placebo n=548	Aducanumab low dose n=543	Absolute Difference (95% CI)	Aducanumab high dose n=547	Absolute Difference (95% CI)
PRIMARY ENDPOINT*										
Change from baseline in CDR-SB	1.56	1.38	-0.18 (-0.47 to 0.11)	1.59	0.03 (-0.26 to 0.33)	1.74	1.48	-0.26 -0.57 to 0.04)	1.35	-0.39 to -0.09)
SECONDARY ENDPOINTS (select)										
MMSE Score Decline	-3.5	03.3	0.2 (-0.3 to 0.7)	-3.6	-0.1 (-0.6 to 0.5)	-3.3	-3.4	-0.1 (-0.7 to 0.5)	-2.7	0.6 (0 to 1.1)
Change in ADAS-Cog13 score	5.14	4.56	-0.58 (-1.58 to 0.42)	4.55	-0.59 (-1.61 to 0.43)	5.16	5.46	-0.7 (-1.76 to 0.36)	3.76	-1.4 to -0.34)
SAFETY	n=532	n=545		n=554		n=544	n=537		n=541	
Serious AE		76 (14%)	1%	79 (14%)	1%	81 (15%)	72 (13%)	-2%	73 (13%)	-2%
ARIA-E	16 (3%)	141 (26%)	23% **NNH≈4**	199 (36%)	33% **NNH≈3**	13 (2%)	140 (26%)	24% **NNH≈4**	188 (35%)	33% **NNH≈3**
Brain microhemorrhage	34 (6%)	89 (16%)	10% **NNH≈10**	104 (19%)	13% **NNH≈7**	37 (7%)	87 (16%)	9% **NNH≈11**	108 (20%)	13% **NNH≈7**

*With early termination, only 959 (58.2%) in **ENGAGE** and 877 (53.5%) in **EMERGE** completed the primary endpoint.
The primary endpoint was met in **EMERGE** (difference of −0.39 for high- dose aducanumab vs placebo [95% CI, −0.69 to −0.09; p=0.012; 22% decrease]) but not in **ENGAGE** (difference of 0.03, [95% CI, −0.26 to 0.33; p=.833; 2% increase]).

STRENGTHS, LIMITATIONS, & UNCERTAINTIES

STRENGTHS:

- Novel mechanism of action aims to target the pathophysiological cause of dementia. Both studies showed statistically significant reductions in amyloid levels (exploratory, in a subset).
- Groups well balanced at baseline.

LIMITATIONS:

- Early termination of the studies resulted in fewer data on which to perform the analyses than was initially planned (though all patients completed at least 6 months).
  - It was also determined after the analysis that two of the assumptions for stopping the trial early were incorrect: 1) that the treatment effects between the studies would be the same, and 2) that the effect of the treatment would stay consistent over time. As such, the final outcomes were deemed inaccurate. It was determined that the trial should not have been terminated early.
- Inconsistency in results between two identically designed trials - In **EMERGE**, a statistically significant slowing of clinical decline was seen in the high-dose arm for the primary endpoint (CDR-SB) and three secondary endpoints (MMSE, ADAS-Cog13, and ADCS-ADL-MCI), demonstrating a consistent benefit of high-dose aducanumab over placebo. However, In **ENGAGE**, the primary and secondary endpoints were not met.
  - The conflicting results of **ENGAGE** make it difficult to infer any clinical relevance of these findings.
- Although **EMERGE** showed statistically significant slowing of clinical decline, it did not reach an MCID of 1 – so clinical meaningfulness is uncertain.
- The adverse event, ARIA-E, may have caused patients and caregivers to become "unblinded" during the study. This may have influenced their subjective reporting of functional and cognitive changes for primary/secondary outcomes.
- The populations in these studies lack diversity, including racial/ethnic diversity, patients with co-morbid conditions, and those on some concomitant medications. Additionally, most patients (~75%) were screened out due to inclusion/exclusion criteria.
  - This limits the generalizability of the data and additional data generation is required.
- Important QOL perspective and adverse events from treatment: Severe AE that investigators reported as ARIA symptoms included headache, confusional state, seizure, and muscle weakness due to cerebral hemorrhage. Additionally, costs and monitoring that is required may limit accessibility.
- There was extensive manufacturer involvement throughout the study.
- Protocol amendment altered the number of patients in the high-dose group that received the 10mg/kg dose (rather than the 6mg/kg dose).
  - This impacted more patient in the **EMERGE** trial than in the **ENGAGE** trial (see *Other notes of interest* below for post-hoc analysis of this as a confounder of results).
  - There was no sensitivity analysis in the trial to look at differences in dose within the arms.

UNCERTAINTIES:

- If trials were not ended early, would there be any difference in outcomes achieved?
- Is more time required to observe clinically important delayed disease progression?
- How clinically significant are amyloid related imaging abnormalities?
- What is the appropriate duration of therapy for people who may start this medication?

Other notes of interest:

Post-hoc Analysis (completed by the manufacturer):[3]

- Modelling suggested possible difference related to protocol amendment in which more patients in **EMERGE** received the higher dose than in **ENGAGE**.

Controversy surrounding the Food and Drug Administration (FDA) approval of aducanumab:[4]

- Even though the FDA's *Peripheral and Central Nervous System Advisory Council* voted against FDA approval, the FDA approved the monoclonal antibody aducanumab (**ADUHELM**) for the treatment of early Alzheimer disease through an accelerated pathway based on reduction in β-amyloid (which was an exploratory surrogate endpoint). This, despite a lack of evidence for clinically important efficacy alongside concerns about adverse effects.

Drug Availability: FDA granted accelerated approval in 2021, Medicare restricted coverage to use in clinical trials only, this contributed to limited uptake. Removed from the market in 2024, & the confirmatory trial that had been required for FDA approval was discontinued. The manufacturer, Biogen, indicated they were working in partnership with the manufacturer of **LEQEMBI** (see **CLARITY AD** Trial Summary) to support that medication instead.[5]

RxFILES RELATED LINKS

- ANTI-AMYLOID MEDICATION FOR ALZHEIMER'S DISEASE: Overview of Landmark Trials https://www.rxfiles.ca/RxFiles/uploads/documents/AD-Summary-of-Trials.pdf
- RxFiles **TRAILBLAZER-ALZ 2** Trial Summary https://www.rxfiles.ca/RxFiles/uploads/documents/ts-TRAILBLAZER-ALZ-2-TRIAL-SUMMARY-2023.pdf

Abbreviations: AD=Alzheimer's disease **ADAS-cog13**=Alzheimer's Disease Assessment Scale Cognitive Subscale–13 items **ADCS-MCI-ADL**=Alzheimer's Disease Cooperative Study–Activities of Daily Living Scale for Mild Cognitive Impairment **AE**=adverse events **ApoE4**=apolipoprotein E4 **ARIA**=amyloid-related imaging abnormalities **ARIA-E**=amyloid-related imaging abnormalities of edema/effusion **CDR-SB**=Clinical Dementia Rating Scale Sum of Boxes **CI**=confidence interval **FDA**=Food and Drug Administration **IV**=intravenous **MCI**=mild cognitive impairment **MCID**=minimal clinically important difference **MMSE**=Mini-Mental State Exam **MRI**=magnetic resonance imaging **n**=number **NNH**=number needed to harm **p**=p-value **PET**=positron emission tomography **QOL**=quality of life **wk**=weeks **yr**=years/years old

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References:

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