ANTI-AMYLOID MEDICATION FOR ALZHEIMER'S DISEASE: Overview of Landmark Trials[1-3] © www.RxFiles.ca Nov 2025

L Regier, BSP BA with M Kurz, E Holmlund, & N Helson, 2024 PharmD Candidates

Bottom line: These anti-amyloid medications generally achieved statistical significance based on their primary outcomes, however, they did not appear to reach a proposed clinically meaningful benefit. The harms (including ARIA-H/E) and the need for regular MRI monitoring limit practical application and add to overall cost of treatment. These novel drugs pose a theoretical disease-progression-altering capacity based on amyloid plaque reduction; however, their clinical value and long-term outcomes remain unclear.

76-week tx duration for each	**TRAILBLAZER-ALZ 2** **Donanemab** KISUNLA (2023)	**CLARITY AD** **Lecanemab** LEQEMBI (2023)	**EMERGE *and* ENGAGE** *Identically Designed RCTs* **Aducanumab** ADUHELM (2022)
Population Highlights	• Included patients with Alzheimer's disease (AD), with mild cognitive impairment or with mild dementia • Mean age across RCTs: ~70-73yr • MMSE across RCTs needed to be in the upper range: ~20-30 (higher score means less impairment; max score on scale = 30) • Population was selective: ~60-75% screened out due to inclusion/exclusion criteria		
Intervention / Comparator	**Donanemab** 1400mg (with 700mg dose titration x first 3 doses) vs placebo IV q4 weeks for 76 weeks	**Lecanemab** 10mg/kg vs placebo IV q2 weeks for 76 weeks	**Aducanumab** low dose (3 or 6mg/kg target dose) vs **aducanumab** high dose (10mg/kg target dose) vs placebo IV q4 weeks for 76 weeks
Outcomes	***See individual RxFiles Trial Summaries for more details:* TRAILBLAZER ALZ 2, CLARITY, EMERGE and ENGAGE**		
	• RCTs achieved statistically significant results in 1° outcome however, differences seen did not meet what would usually be considered the minimal clinically important difference (MCID)		• 1 RCT (**ENGAGE**) had non-significant results • 1 RCT (**EMERGE**) originally appeared to have no benefit, but then re-analysis of the full dataset suggested statistically significant results (in only the high dose arm - unclear why difference between the two trials, ?note difference in placebo arms[5]) • Neither RCT achieved a clinically significant change in 1° outcome
CDR-SB (An 18-point scale to assess cognition & function; lower score = ↓ impairment)	**CDR-SB** (2º outcome): - 0.68 point difference vs placebo	**CDR-SB** (1º outcome) - 0.45 point difference vs placebo	**CDR-SB** (1º outcome) – high dose **EMERGE**: - 0.39 point difference vs placebo **ENGAGE**: + 0.03 point difference vs placebo
	The commonly suggested minimally important difference (MCID) on the CDR-SB scale is 1 point. None of the RCTs achieved this.		
iADRS (A 144-point scale to assess cognition & function; higher score = ↓ impairment)	**iADRS** (1º outcome): + 2.92 point difference vs placebo - to assess cognition & function (calculated as composite of *ADCS-iADL* + *ADAS-Cog 13* scores). - did not achieve pre-determined minimum important difference (MCID in AD with mild cognitive impairment=5; MCID in AD with mild dementia=9)	Not applicable – not reported as a composite.	
Other	Other cognitive assessments conducted showed similarly small differences in score.	Similar relative improvements seen in other measures of cognition and functioning.	Conflicting results between 2 RCTs in measures of cognitive and functional improvement; small, statistically significant improvement (not above the threshold for clinically significant benefit) for high dose in **EMERGE**.
Amyloid Plaque Reduction	All RCTs reported a reduction in amyloid plaques, which is of interest given the proposed pathophysiology of Alzheimer's disease. However, this is a **surrogate endpoint of interest** compared to the clinical endpoints above of relatively more importance.		
Notable Harms	**All RCTs had adverse events (AE) of concern**. ARIA-H and ARIA-E (ARIA=amyloid related imaging abnormalities, ARIA-H=ARIA with microhemorrhages, ARIA-E=ARIA with edema): **NNH≈3 to 12**/76wk. Other AE of interest included infusion reactions, falls, & reduction in brain volume. **Serious Adverse Events** (SAE) were more common in treated group than placebo (**NNH≈37 to 62**/76wk), as were discontinuation rates. *See individual RxFiles Trial Summaries for additional details:* **TRAILBLAZER ALZ 2, CLARITY, EMERGE and ENGAGE**		
Additional Considerations	**Drug Cost**: **$32,000** USD/year - FDA approved 2024 (previously denied accelerated approval due to lack of data beyond 12 months of therapy) - Submitted to HC in 2024 (under review as of Nov 2025)	**Drug Cost**: **$26,500** USD/year - FDA approved 2023 - HC approved (with conditions) Oct 2025, not yet marketed as of Nov 2025 - Requires imaging which adds to the burden & costs imposed on the health care system	- FDA approved 2021; however, removed from the US market in Feb 2024 (manufacturer reportedly focusing on marketing **LEQEMBI**) - Withdrew application from HC due to conflicting trial data & likelihood of not receiving approval[4]
	Cost of therapy is high, especially relative to the apparent lack of clinically important benefit alongside concerns about harms. **Diagnostic supports** (PET Scans and MRI) were part of the protocols and required for therapy as part of diagnostic criteria for trial enrollment as well as monitoring for harm throughout treatment, adding to the **burden on financial and human resources**. When analyzing the **Kaplan Meier Curves** for the RCTs, one way to look at the potential benefit is that the decline in scores for the treated group lags the placebo group by about 2 months. This, with the caveat that the difference gained is still less than the MCID. In other words, one may gain about 2 months of slowed decline that is so minimal it is not likely to be noticeable. Yet, there may be potential for some patients to benefit more than the group mean. Analysis of other agents in trials (e.g. bapineuzumab, gantenerumab, solanezumab) have not yielded meaningful improvement.[6]		

Abbreviations: **AD**=Alzheimer's disease **ADAS-Cog**=Alzheimer's Disease Assessment Scale-Cognitive Subscale **ADCS-iADL**=Alzheimer's Disease Cooperative Study–Instrumental Activities of Daily Living **AE**=adverse events **ARIA**=amyloid related imaging abnormalities **ARIA-H**=ARIA with microhemorrhages **ARIA-E**=ARIA with edema **CDR-SB**=Clinical Dementia Rating-Sum of Boxes **FDA**=Food and Drug Administration **HC**=Health Canada **iADRS**=Integrated Alzheimer's Disease Rating Scale **IV**=Intravenous **kg**=kilogram **MCI**=Mild Cognitive Impairment **mg**=milligram **MCID**=minimal clinically important difference **MMSE**=Mini-Mental State Examination **MOA**=mechanism of action **MRI**=Magnetic Resonance Imaging **NNH**=number needed to harm **PET**=Positron Emission Tomography **RCT**=randomized controlled trial **rxn**=reaction **SAE**=serious adverse event(s) **tx**=treatment **USD**=United States Dollars **wk**=week(s) **yr**=years old

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References for ANTI-AMYLOID MEDICATION FOR ALZHEIMER'S DISEASE: Overview of Landmark Trials

1. Haeberlein BS, Aisen PS, Barkhof F, et al. Two Randomized Phase 3 Studies of Aducanumab in Early Alzheimer's Disease. J Prev Alzheimers Dis 2022;9(2):197–210. https://doi.org/10.14283/jpad.2022.30.
2. Sims JR, Zimmer JA, Evans CD, et al. Donanemab in Early Symptomatic Alzheimer Disease: The TRAILBLAZER-ALZ 2 Randomized Clinical Trial. JAMA. 2023;330(6):512–527. doi:10.1001/jama.2023.13239.
3. Van Dyck CH, Swanson CJ, Aisen P, et al. Lecanemab in Early Alzheimer's Disease. N. England J.M. 2023; 388(1): 9-21. doi:10.1056/NEJMoa2212948.
4. Biogen Canada. Biogen Canada announces intention to transition Aduhelm access program in Canada [Press release]. (2022, June 9). Available from: https://www.biogen.ca/en-ca/news/2022-06-09-news.html.
5. Knopman DS, Jones DT, & Greicius MD. Failure to demonstrate efficacy of aducanumab: An analysis of the EMERGE and ENGAGE trials as reported by Biogen, December 2019. *Alzheimer's & dementia : the journal of the Alzheimer's Association*, 2021;*17*(4):696–701. https://doi.org/10.1002/alz.12213.
6. Ackley SF, Zimmerman SC, Brenowitz WD, et al. Effect of reductions in amyloid levels on cognitive change in randomized trials: instrumental variable meta-analysis. BMJ. 2021; 372:n156. doi: http://dx.doi.org/10.1136/bmj.n156.