Lecanemab in Early Alzheimer's Disease[1]

CLARITY AD Trial Summary (2023)

SUMMARY

In **CLARITY AD,** patients with either mild cognitive impairment or mild dementia due to Alzheimer's disease found small statistically significant improvements in terms of cognition and functioning as measured by the CDR-SB score (-0.45 points), although the clinical significance of this result is not certain (see "minimal clinically important difference" below).

- On the 18-point CDR-SB scale, 0.45 points is a smaller interval than any individual severity category.
  - It has been proposed that a score of 1 represents a minimal clinically important difference on the CDR-SB scale, and as such the observed difference of 0.45 does not meet this threshold.[4]
- The medication effectively contributes to amyloid plaque clearance, however this surrogate marker does not seem to translate into clinical improvement.
- Adverse event rates are high, with any treatment-related AE having a **NNH≈4** and discontinuation due to AE having a **NNH≈25** over 76 weeks.

Bottom Line:

- Lecanemab showed statistical but not clinically important improvement in cognitive and functional score of people with **mild** cognitive impairment or dementia in AD. Since adverse effects include amyloid related imaging abnormalities with cerebral edema and hemorrhage (ARIA-E & -H) as well as and infusion-reactions, the risk of harms and the costs associated with the drug itself ($26,500 per year in the US) along with required monitoring (e.g. MRI/PET scan), likely exceed this marginal benefit. Further study is required to evaluate the clinical utility of this medication over the longer term alongside the adverse events.

BACKGROUND

- A key distinguishing feature of Alzheimer's disease (AD) is the presence of beta-amyloid plaques in the brain.[5]
- Newer biologic drugs such as lecanemab aim to clear amyloid from the brain, as it is theorized this will affect the underlying pathology of the disease.[1]
- While it is theorized that beta-amyloid plaques may play a causative role in the Alzheimer's disease, previous drug therapies have focused on increasing levels of acetylcholine in the brain or antagonizing NMDA receptors to treat symptoms.[1]
- Existing drug therapies for Alzheimer's disease have shown only modest benefits, with mild impact on disease progression and many associated side effects.[5]

CLARITY AD METHODS (SEE ORIGINAL ARTICLE/SUPPLEMENT FOR FULL CRITERIA)

DESIGN: Double blind, randomized, placebo-controlled, multi-centre (235 sites) trial. Randomization was completed by a computer-generated procedure with independent statistician review.

- Enrollment occurred from March 2019 through March 2021.
- Randomization was stratified by geographic location (North America, Europe, Asia-Pacific), symptom severity at enrollment, use of other approved medications for Alzheimer's disease, and apolipoprotein E carrier status (ApoE carriers have a higher risk of amyloid related imaging abnormalities).
- All individuals participating in and facilitating the trial were blinded to treatment groups. Formal unblinding only occurred in the cases where it was required due to patient medical status.
- A modified intention-to-treat (m-ITT) analysis was used for the primary outcome, including participants who received at least one dose of lecanemab or placebo, had a baseline assessment, and had one primary outcome assessment.
- Design, funding, and writing assistance for the study was provided by the sponsor (Eisai Co).
- The CDR-SB score (1° outcome) measures patient cognition as well as patient functioning, through caregiver assisted interviews.

INTERVENTION: Lecanemab 10mg/kg IV q2wk vs placebo

POPULATION:

- **INCLUSION** (select – see other notes for full criteria)**:** Age 50-90, mild cognitive impairment due to Alzheimer's disease or mild Alzheimer's dementia, impairment in episodic memory of at least 1 standard deviation below the age-appropriate average, positive indication of brain amyloid.
- **EXCLUSIONS** (select – see other notes for full criteria)**:** Presence of other conditions that may contribute to cognitive impairment, contraindication to MRI scanning, signs of dementia other than Alzheimer's, geriatric depression scale score of 8 or greater, uncontrolled medical conditions that may affect results.

POPULATION: Screened: n=5967; Enrolled: 1795 participants randomized to lecanemab (n=898) or placebo (n=897), 1734 in the m-ITT population.

- Mean age 71.2 years, 52% female, 77% white, 2.5% black, 17% Asian, mean CDR-SB score of 3.2.
- 38% mild dementia due to Alzheimer's disease, 62% mild cognitive impairment (MCI) due to Alzheimer's disease.

OUTCOMES – over 76 weeks:

- **Primary:** change from baseline at 18 months in the score on the Clinical Dementia Rating–Sum of Boxes (CDR-SB; range, 0 to 18, with higher scores indicating greater impairment).
- **Secondary** (select): change from baseline at 18 months in the following: amyloid burden on PET (measured in centiloids), ADAS-cog14 (range 0 to 90, with higher scores indicating greater impairment), ADCOMS (range, 0 to 1.97, with higher scores indicating greater impairment), ADCS-MCI-ADL (range, 0 to 53, with lower scores indicating greater impairment).

RESULTS

follow up over 18 months (1.5yr)

TABLE 1: EFFICACY & SAFETY (m-ITT population used)

Clinical Endpoints	Lecanemab 10mg/kg n=859	Placebo n=875	Absolute Difference (95% CI)	Comments
PRIMARY ENDPOINT				
Change from baseline in CDR-SB	1.21	1.66	-0.45 (95% CI: -0.67 to -0.23)	• 19-point scale; higher score=greater impairment. • MCID is considered a change of ≥1 in AD. • Same scale used in trials for donanemab & aducanumab.
SECONDARY ENDPOINTS (select)				
Mean change in amyloid "burden" on PET	-55.5 centiloids	3.6 centiloids	-59.1 centiloids (95% CI: -62.64 to -55.60)	• Centiloids measure the percent of amyloid protein present in the brain (surrogate marker).
Mean change in ADAS-cog14 score	4.14	5.58	-1.44 (95% CI: -2.27 to -0.61)	• 91-point scale; higher score=greater impairment
Mean change in ADCOMS	0.164	0.214	-0.05 (95% CI: -0.074 to -0.027)	• O to 1.97-point scale; higher score=greater impairment. • MCID: 0.05 for MCI, 0.1 for mild dementia
SAFETY	**Full treatment group** n=898	**Full placebo group** n=897		
Any treatment-related AE	401 (44.7%)	197 (22%)	22.7% **NNH≈4**	• Driven by infusion rxn, ARIA, headache, & falls
Treatment D/C due to AE	62 (6.9%)	26 (2.9%)	4% **NNH≈25**	• Reasons not specified
Any ARIA-E	113 (12.6%)	15 (1.7%)	10.9% **NNH≈9**	• Deemed serious in 0.8% of lecanemab vs 0% in placebo • Absolute rates occurred most often in APOE4 homozygotes
Any ARIA-H	155 (17.3%)	81 (9%)	8.3% **NNH≈12**	• % deemed serious not reported • Absolute rates occurred most often in APOE4 homozygotes
Infusion-related reaction	237 (26.4%)	66 (7.4%)	19% **NNH≈5**	• Deemed serious in 1.2% of lecanemab vs 0% in placebo
Other serious AE included: atrial fibrillation (0.7% lecanemab vs 0.3% pl), syncope(0.7% lecanemab vs 0.1% pl), & angina pectoris (0.7% lecanemab vs 0% pl).				

STRENGTHS, LIMITATIONS, & UNCERTAINTIES

STRENGTHS:

- Unlike the **ENGAGE** trial for aducanumab looking into the effect of anti-amyloid antibodies, **CLARITY AD** was able to show a statistically significant difference in a clinical measurement of symptoms of Alzheimer's disease.
- The patient population studied was relatively large in this trial and had a good ratio of male-to-female subjects.
- The trial was adequately powered to detect a difference, compensating for an up to 20% discontinuation rate, which was greater than the 17.2% observed trial discontinuation rate.
- Therapy was continued regardless of whether amyloid plaque cleared (compared to how treatment was discontinued early in **TRAILBLAZER-ALZ 2)**

LIMITATIONS:

- 3555/5967 (59.6%) of potential participants were screened out because of exclusion criteria or not meeting inclusion criteria. This limits applicability to the general population (external validity).
  - They excluded "uncontrolled medical conditions" and did not report on comorbidities in the baseline population.
- This trial used a modified ITT analysis, which excluded more patients from the lecanemab group (4.4%) than the placebo group (2.5%)
  - Although the criteria for the m-ITT analysis seem reasonable, they present the opportunity for bias to enter the trial as they decrease the effects of randomization and affect the groups in an unequal manner.
  - A sensitivity analysis accounting for this reveals a comparable, albeit slightly smaller, difference between group CDR-SB scores.
- This trial followed patients for 18 months, whereas Alzheimer's disease may continue to develop over several years.[2]
- With the m-ITT population including those with at least one primary outcome assessment, the value of randomization is diminished (i.e. loses the confidence and rigor of a true ITT analysis).

UNCERTAINTIES:

- How many patients would need to be treated to see a clinically significant benefit?
  - An answer would require the authors to define what they believe a meaningful benefit is, and then report how many patients achieve this benefit and how many do not.
  - There is suggestion that the CDR-SB score difference achieved by lecanemab compares to one that would be achieved by acetylcholinesterase inhibitors. The NNT for acetylcholinesterase inhibitors is 12 for a minimal benefit and 42 for a marked benefit (although current AD medications are not used in the context of mild cognitive impairment).[6,7]
- What was the full effect of unblinding on the results of the primary outcome?
  - A sensitivity analysis presented in the trial's supplementary appendix investigated the effects of unblinding due to ARIA-E, but not ARIA-H.[4] Unblinding may have influenced assessors and caregivers, whose perspectives influence CDR-SB scoring.
  - Much higher rates of infusion reactions in the lecanemab group may have essentially unblinded participants and investigators to treatment groups
- The effects and potential benefits and harms of lecanemab in patients over a period of longer than 18 months are unknown.
  - Will benefits continue to increase over time? Will harms?
- How did brain volume change over the course of this trial?
  - A previous trial showed decreasing brain volume and increasing ventricular volume with lecanemab use.[6]
  - Do reductions in brain volume have detrimental long-term effects?
- Does lecanemab alter the course of Alzheimer's disease?
- How does lecanemab compare to acetylcholinesterase inhibitors, NMDA antagonists, and other anti-amyloid therapies, especially when considering longer duration of therapy, costs, and potential harms?
- Would therapy with lecanemab be practical (especially in Canada) with the requirement for 4 MRI scans and 1 PET scan within the first 2 years of therapy? What infrastructure changes will be needed to support users of this drug?
  - How do these requirements add to the overall costs of the drug for individuals and health care systems?

Other notes of interest:

Drug Cost: lecanemab **LEQEMBI $26,500** USD/year (plus the cost associated with assessment for appropriateness & ongoing monitoring e.g. PET/MRI scans, APOE4 genotyping). IV dose infused over approximately one hour (at infusion centre). Approved with conditions (to assess long-term safety) by Health Canada in Oct 2025 (but not yet marketed Nov 2025).

- An open-label extension trial is ongoing from this study to assess longer-term safety outcomes (90% of trial participants continued, goal for tx ~4 years).[10] However, safety analysis including those who received at least one dose – would be anticipated to under-report AE outcomes may limit applicability to someone receiving the dose regularly.
- Subcut administration (**LEQEMBI IQLIK** FDA approved auto-injector Aug 2025, dose: 360mg subcut q1wk) has also been studied as part of open-label extension (monograph states 49 patients), preliminary results suggest this route to have fewer systemic injection-related adverse events (e.g. headache, fever, fatigue).

FULL INCLUSION CRITERIA: 50-90 years old, mild cognitive impairment due to Alzheimer's or mild Alzheimer's related dementia (based on global CDR score), objective impairment in episodic memory evidenced by 1 standard deviation below age adjusted mean, brain amyloid indicated by positive biomarker test, MMSE >/= 22, BMI >17 and <35, must be on a stable dose of other Alzheimer's medications for 12 weeks if on other therapy, needs a study support partner, informed consent, willing and able to comply.

FULL EXCLUSION CRITERIA: Pregnancy or breastfeeding, of childbearing potential without use of highly effective birth control during study and in 28 days before and after the study, any contributing neurologic condition other than Alzheimer's, history of TIA in the last 12 months, psychiatric diagnosis that could interfere with study, geriatric depression score of 8 or greater, contraindications to MRI, evidence of clinically significant brain lesions, significant pathological findings on MRI of the patient's brain, hypersensitivity, uncontrolled immunologic disease, uncontrolled bleeding disorder, TSH above normal range, low vitamin B12, HIV positive, any significant finding on examination that the principle investigator determines requires further treatment or may interfere with the study, history of malignant neoplasms within 3 years of being screened for the study, suicidal ideation or behaviour, substance abuse within last 2 years, uncontrolled medical conditions that may affect results, taking prohibited medications, participation in a study with receipt of monoclonal antibodies or vaccines within last 6 months (or 1 year for anti-amyloid antibodies), prior exposure to lecanemab, receipt of new Alzheimer's drug in a clinical trial in the last 6 months, participation in new medication or device study in 8 weeks or 5 half-lives (whichever is longer) before trial unless placebo was received, planned surgery requiring general anesthesia during the study, severe vision or hearing impairment preventing assessment.

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
- RxFiles **EMERGE** & **ENGAGE** Trial Summary https://www.rxfiles.ca/RxFiles/uploads/documents/ts-EMERGE-ENGAGE-TRIAL-SUMMARY-2022.pdf

Abbreviations: AD=Alzheimer's disease **ADAS-cog**=Alzheimer's Disease Assessment Scale Cognitive Subscale **ADAS-cog14**=Alzheimer's Disease Assessment Scale Cognitive Subscale–14 items **ADCOMS**=Alzheimer's disease composite score **ADCS-MCI-ADL**=Alzheimer's disease cooperative study–Activities of Daily Living Scale for Mild Cognitive Impairment **AE**=adverse events **APOE4**=apolipoprotein E4 **ARIA-E**=amyloid-related imaging abnormalities of edema/effusion **ARIA-H**=amyloid-related imaging abnormalities of cerebral microhemorrhages **AUD**=alcohol use disorder **BMI**=body mass index **CDR**=common drug review **CDR-SB**=Clinical Dementia Rating Scale Sum of Boxes **CI**=confidence interval **CMS**=Centers for Medicare and Medicaid **CSF**=cerebrospinal fluid **D/C**=discontinue(d) **FDA**=Food and Drug Administration **HIV**=human immunodeficiency virus **iADL**=Instrumental Activities of Daily Living **iADRS**=integrated Alzheimer's Disease Rating Scale **ITT**=intention to treat **IV**=intravenous **LSM**=least squares mean **MCI**=mild cognitive impairment **MCID**=minimum Clinically Important Difference **m-ITT**=modified intention to treat **MMSE**=Mini-Mental State Exam **MRI**=magnetic resonance imaging **NMDA**=N-methyl-D-Aspartate **NNH**=number needed to harm **NNT**=number needed to treat **PET**=positron emission tomography **PI**=placebo **rxn**=reaction **SUD**=substance use disorder **TIA**=transient ischemic attack **TSH**=thyroid stimulating hormone **tx**=treatment **wk**=weeks **yr**=years

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