Donanemab in Early Symptomatic Alzheimer's Disease[1]

TRAILBLAZER-ALZ 2 Trial Summary (2023)

SUMMARY

In **TRAILBLAZER-ALZ 2**, patients with early-stage Alzheimer's who received donanemab q4wk vs placebo for 76 weeks:

- Had a small but statistically significant improvement (slowed decline) of iADRS scores (functional & cognitive composite scale of 0-144) in the intervention group, however this difference did not meet the minimal clinically important difference.
  - Donanemab: −6.02 (95% CI, −7.01 to −5.03)
  - Placebo: −9.27 (95% CI, −10.23 to −8.31)
  - Difference: 2.92 (95% CI, 1.51-4.33]; P < .001)
  - MCID: 5 points in AD; 9 points in AD with mild dementia
- 80.1% (95% CI: 76.12% to 83.62%) of patients achieved a statistically significant reduction of amyloid plaque levels (<11 centiloids on one reading, or <24 centiloids on two consecutive readings) and were switched to placebo before 76 weeks. Since this is a surrogate outcome and based on the iADRS data, it is uncertain how clinically significant this reduction is.
- Participants on donanemab were more likely to experience amyloid-related imaging abnormalities with edema/effusion (ARIA-E) (**NNH≈4**), microhemorrhages (**NNH≈7**) and infusion reactions (**NNH≈12**) over the 76 weeks.
  - 112 (13.1%) patients on donanemab discontinued therapy due to AE, compared to 38 (4.3%) in the placebo group.
  - Patients on donanemab also had an approximate mean reduction in brain volume of 7cm^3.

Bottom Line:

- Based on this data, donanemab lacks the efficacy to produce a clinically significant benefit in patients with early-stage AD and poses a significant risk of adverse events. Although the duration of the study may be insufficient to observe a clinically meaningful effect, the lack of benefit is consistent with other amyloid-targeting monoclonal antibody trials. Additionally, the lack of consistent therapy duration among the intervention arm of the trial (i.e. could stop early based on clearance of amyloid plaque) limits the applicability of the results, especially concerning the safety data.

BACKGROUND

- Donanemab is a monoclonal antibody that received approval by the FDA in 2024 and has been submitted for review by Health Canada for the indication of slowing the progression of Alzheimer's disease (AD). It targets insoluble β-amyloid proteins present in amyloid plaques.
- The build-up of amyloid protein in the brain that normally reside in the CSF produces amyloid plaques characteristic of AD and are responsible for the death/atrophy of brain cells, producing cognitive decline. The brain amyloid plaques can develop for up to 15 years before the development of AD symptoms.[2]
- Eli Lilly applied for accelerated approval but was denied by the FDA due to a limited number of patients who received 12 months of therapy in the phase 2 trials.[3]
  - Eli Lily reported that many patients in the phase 2 trials had their therapy discontinued due to reaching a pre-specified target amyloid level before the 12-month mark of therapy.[3]
- Two other therapies have been able to significantly reduce amyloid plaques in the brain, but their effects on disease progression have been controversial (aducanumab and lecanemab).
- A dose titration of 700mg for the first three doses at the initiation of therapy was added to attempt to mitigate an increased incidence of ARIA-E that was observed in the phase 2 trials.
- Patients were grouped into low/moderate tau protein and high tau protein groups for analysis. The high tau group was only reported in a combined group with the low/moderate tau groups which could mask the more negative results that occurred in the high tau group.
  - Tau proteins are responsible for the neurofibrillary tangles present in AD. Higher levels of tau protein are associated with increases in brain cell damage/death and progressive cognitive decline
- The iADRS (integrated Alzheimer's disease rating scale) was used to measure the progression of Alzheimer's disease. This scale ranks patients from 0-144 (lower=more severe impairment) and utilizes both iADL and ADAS-Cog scores to calculate an iADRS score.

TRAILBLAZER-ALZ 2 METHODS (SEE ORIGINAL ARTICLE/SUPPLEMENT FOR FULL CRITERIA)

DESIGN:

- Block randomized (block size of 4), double-blind, placebo-controlled, international, multicentre (277 sites in 8 countries), 18-month phase 3 trial. Sponsored by Eli Lily and Co. Enrollment occurred from June 19th, 2020 until November 5th, 2021.

INTERVENTION: **Donanemab** 700mg IV q4wk x 3 doses then 1400mg IV q4wk thereafter vs placebo IV q4wk (1:1 stratification)

- Discontinued early if a significant reduction in amyloid plaque was achieved, liver dysfunction, suicidal ideation or related behaviours, or ECG changes.

POPULATION:

- **INCLUSION:** Age 60-85 years at the time of enrollment, reported gradual and progressive changes in memory function for 6+ months, MMSE scores of 20-28 (inclusive), amyloid pathology (>37 centiloids), presence of tau pathology, and have a study partner in contact with the participant for at least 10 hours each week and able to accompany the participant to visits or available by phone.
- **EXCLUSIONS:** Presence of amyloid-related imaging abnormalities of edema/effusion, more than 4 cerebral microhemorrhages, more than 1 area of superficial siderosis or intracerebral hemorrhage greater than 1cm or severe white matter disease on MRI, neurologic disorder other than AD or have a history of AUD or SUD within past 2 years.
  - 72.9% were screened out due to failure to meet MMSE score or tau/amyloid protein criteria.

POPULATION Screened: n=8240; Enrolled: n=1736; 57.3% female with a mean age of 73yr

- **Race/ethnicity:** 91.4% white, 6.0% Asian, 2.3% black, 0.1% American Indigenous/Alaskan Native, 0.1% mixed
- **Geographic region:** 72.1% were American
- **Education:** 71.6% were educated for 13 or more years
- **AD therapy:** 61% were on AChEi/memantine (no significant difference between groups).
- **Plasma P-tau217** (a marker of amyloid and tau-pathology): More common in the intervention group than the placebo group in both subsets (18.5% vs. 15.4% in the combined group, 17.7% vs. 11.3% in the low/medium tau group)

Discontinuation of therapy for AE occurred if:

- ARIA-E: Severity of ≥3 within first three doses, patient experienced symptomatic ARIA-E, or severity of 4-5 after dose titration
- ARIA-H: >4 new microhemorrhages or >1 superficial siderosis within the first 3 doses, >10 new microhemorrhages or >2 new superficial sideroses from baseline or patient was symptomatic for ARIA-H
    - If the patient stabilized (relief of symptoms, no new superficial siderosis, ≤1 new microhemorrhage or edema resolves), then could restart therapy.

OUTCOMES – over 76 weeks:

- **Primary:** change in integrated Alzheimer Disease Rating Scale (iADRS) score from baseline
- **Secondary**: Numerous, including change in the Clinical Dementia Rating Scale (CDR-SB) score, MMSE, brain amyloid plaque deposition, change in volumetric MRI measures.

RESULTS

follow up over 76 weeks

TABLE 1: EFFICACY & SAFETY

Clinical Endpoints	Donanemab 1400mg (low/moderate Tau) n=418	Placebo (low/moderate tau) n=444	Difference (low/moderate tau)	Comments
PRIMARY ENDPOINT				
LSM change in iADRS score from baseline to 76 weeks	-6.02 (95% CI: -7.01 to -5.03)	-9.27 (95% CI: -10.23 to -8.31)	3.25 (95% CI 1.88 to 4.62)	• 145-point scale; lower score=greater impairment. • The differences between placebo and donanemab do not meet the MCID value of 5, even at the upper limit of the CI. • The combined tau group values for all endpoints produced a smaller difference from placebo than the low/moderate tau groups. This indicates that the high tau group performed worse than the low/moderate tau group.
SECONDARY ENDPOINTS				
Change from baseline in CDR-SB	1.16 (95% CI: 0.97 to 1.35)	1.84 (95% CI: 1.65 to 2.02)	-0.68 (95% CI: -0.94 to -0.42)	• 19-point scale; higher score=greater impairment. • MCID is considered a change of ≥1 in AD. • Same scale used in trials for lecanemab & aducanumab.
Change from baseline in MMSE Score	-1.61 (95% CI: -1.89 to -1.33)	-2.09 (95% CI: -2.36 to -1.81)	0.48 (95% CI: 0.09 to 0.87)	• 31-point scale; lower scores=greater impairment. • The small differences observed in this scale are consistent with the minor effect seen with other mental status scales assessed.
Change in brain amyloid plaque deposition from baseline through week 76 as measured by florbetapir F18 PET scan	-88.0 centiloids (95% CI: -90.20 to -85.87)	0.2 centiloids (95% CI: -1.91 to 2.26)	88.2 centiloids (95% CI: not reported)	• Centiloids measure the percent of amyloid protein present in the brain. Theoretically, removing this protein could prevent further damage to the brain cells caused by the amyloid plaque, thus slowing the progression of AD.
Mean change in volumetric MRI measures from baseline through week 76	-24cm^3 (95% CI: -23 to -25)	-17cm^3 (95% CI: -16 to -18)	-7cm^3 (absolute data not reported)	• Concerning adverse effect to be monitored for in other trials assessing anti-amyloid therapies
SAFETY*	**Full treatment group** n=853	**Full placebo group** n=874		
Treatment discontinuation due to AE	112 (13.1%)	38 (4.3%)	8.8% **NNH≈11**	• Reasons: infusion related rxn (3.6 vs 0%), ARIA-E (2.5 vs 0.3%), ARIA-H (0.8 vs 0.2%), & hypersensitivity (0.5 vs 0%)
Any ARIA	314 (36.8%)	130 (14.9%)	21.9% **NNH≈4**	• ARIA-E: 205 (24%) vs 18 (2.1%) • ARIA-H: 268 (31.4%) vs 119 (13.6%) • Absolute rates occurred most often in APOE4 homozygotes
Serious ARIA-E	13 (1.5%)	0 (0%)	1.5% **NNH≈66**	• Serious ARIA-H: 4 (0.005%) vs 0 (0%)
Infusion-related reaction	74 (8.7%)	4 (0.5%)	8.2% **NNH≈12**	• Most during/in 30min post & between 2nd to 5th infusions
*Trial not designed to detect statistically significant differences in safety-related endpoints, may not accurately reflect AE since treatment duration not consistent.				

STRENGTHS, LIMITATIONS, & UNCERTAINTIES

STRENGTHS:

- The patient population studied is large in this trial and has a good ratio of male-to-female subjects
- Patients were on similar concomitant therapies for AD, so no treatment-related differences between the groups anticipated
- The trial was adequately powered to compensate for an up to 30% discontinuation rate, which was greater than the 26% observed discontinuation rate
- Based on secondary outcome measures, donanemab appears to substantially decrease amyloid plaque levels, which theoretically could provide benefit in slowing the progression of AD
- Based on data provided by the corresponding author, an NNT≈11 was observed in preventing a meaningful within-patient change in iADRS score

LIMITATIONS:

- The assessment tool used to measure the progression of cognitive decline in Alzheimer's disease was developed by several stakeholders/employees of Eli Lily.[5] The authors reported that the iADRS was to be developed to detect more sensitive changes in cognitive function produced by Alzheimer's therapies.[5]
- Dose durations were highly variable when using centiloid scores to assess whether the drug has reached its maximal effect and should be discontinued. This wide variability makes it difficult to assess the true safety and efficacy profile of the drug because some patients were able to discontinue therapy before 6 months, while others still had not reached the centiloid target after 18 months.
    - In the combined treatment group, 29.7% had amyloid clearance at 24wk and 76.4% had amyloid clearance at 76wk.
- The trial duration may not be long enough to observe a true clinical benefit
- High tau group data was not reported individually in the manuscript, data can be extrapolated from the combined tau group data but was not analyzed separately (some provided in the supplement). Given the combined group data on efficacy has less of a difference than the low/moderate tau group, we can presume the results from the high tau group were less impressive than the combined group data
- The study population did not include a diverse background of subjects with most patients being of white ethnicity and American.
    - Supplementary subgroup analysis noted no statistical benefit in patients of Asian or Black/African American race (wide confidence intervals).
- A significant proportion of patients discontinued the study in both intervention and placebo groups: 231 (26.9%) in donanemab & 173 (19.7%) in placebo.
- The data on CDR-SB differences did not meet the MCID when compared to placebo.

- Clinically, it is unfeasible to conduct MRIs with the same frequency as was done in the trial to determine which patients should receive therapy and to monitor for the development of ARIA. Additionally, it may also be unfeasible to conduct a PET scan within an appropriate timeframe to determine if the amyloid plaque has resolved sufficiently and assess if therapy can be discontinued. This increases the risk of overtreatment and thus, adverse effects.
- Discontinuation thresholds for ARIA during the titration period (first three doses) are significantly lower than the remainder of the dosage interval. This was reportedly done to lower the incidence of ARIA-E, but having inconsistent thresholds throughout the dosing period would presumably impact the discontinuation rate
- Potential for unblinding due to AE.
- Presumably, a significant proportion of patients experienced a temporary hold of treatment due to ARIA-related adverse effects, however this data was not provided.

UNCERTAINTIES:

- Amyloid plaque is a surrogate marker. The small effect on disease progression observed from clearing amyloid protein in the brain raises questions regarding whether amyloid plaques are a causative factor or a secondary marker of Alzheimer's progression, and to what extent clearing these plaques is clinically beneficial to the patient. Additionally, would targeting all forms of amyloid plaques provide a greater effect on cognitive function, and would it significantly impact the adverse effect profile?
- Would targeting neurofibrillary tangles +/- amyloid plaques provide a greater prevention of cognitive decline when compared to amyloid plaques alone?
- Whether the differences in the plasma p-tau217 levels between the placebo and intervention groups would have an impact on the efficacy of therapy? Presumably, the intervention group having higher levels than the placebo group could enhance the observed effect of the drug to a greater extent than the placebo group.
- Do amyloid protein levels resurge in patients who discontinue therapy once their plaque levels are below a certain level? if so, how quickly do they resurge?
- Amyloid beta protein reportedly begins to deposit 15 years before symptoms of Alzheimer's are present.[2] Could this drug still be able to prevent progression in the long term if amyloid plaques do not quickly redevelop post-therapy discontinuation?
- How clinically significant is the development of ARIA-E/H?

Other notes of interest:

Drug Cost: donanemab-azbt **KISUNLA $32,000** USD/year (not to mention the financial and human resource costs associated with monitoring e.g. PET scan, MRI, APOE4 genotyping).

TRAILBLAZER-ALZ 5 & **6** RCTs underway to assess safety outcomes. Preliminary data from **TRAILBLAZER-ALZ 6** resulted in an FDA dose labelling change in July 2025 to reduce risk of ARIA. Dosing changed to: donanemab 350mg IV x1, then 700mg IV x1, then 1050mg IV x1, each given q4wk, then 1400mg IV q4wk thereafter.

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 **CLARITY-AD** Trial Summary https://www.rxfiles.ca/RxFiles/uploads/documents/ts-CLARITY-AD-TRIAL-SUMMARY-2023.pdf
- RxFiles **EMERGE** & **ENGAGE** Trial Summary https://www.rxfiles.ca/RxFiles/uploads/documents/ts-EMERGE-ENGAGE-TRIAL-SUMMARY-2022.pdf

Abbreviations: AChEi=acetylcholinesterase inhibitors **AD**=Alzheimer's disease **ADAS-Cog**=Alzheimer's Disease Assessment Scale Cognitive Subscale **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 **CDR-SB**=Clinical Dementia Rating Scale Sum of Boxes **CI**=confidence interval **CMS**=Centers for Medicare and Medicaid **CSF**=cerebrospinal fluid **FDA**=Food and Drug Administration **iADL**=Instrumental Activities of Daily Living **iADRS**=integrated Alzheimer's Disease Rating Scale **IV**=intravenous **LSM**=least squares mean **MCID**=minimal clinically important difference **min**=minutes **MMSE=**Mini-Mental State Exam **MRI**=magnetic resonance imaging **NNH**=number needed to harm **NNT**=number needed to treat **rxn**=reaction **PET**=positron-emission tomography **RCT**=randomized controlled trial **SUD**=substance use disorder **wk**=weeks **yr**=years old

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References:

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