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Letter to the Editor

Stage-Specific Efficacy of Lecanemab and Donanemab in Early Alzheimer's Disease: An Indirect, Comparative Interpretation of Phase 3 Trials

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The development of disease-modifying monoclonal antibodies targeting amyloid-β (Aβ) has marked a significant advancement in Alzheimer's disease (AD) therapeutics. Among these, lecanemab and donanemab have demonstrated robust efficacy in phase 3 clinical trials—Clarity AD[1] and TRAILBLAZER-ALZ 2,[2] respectively—showing that sustained amyloid clearance can translate into meaningful clinical slowing of cognitive and functional decline. This summary compares the stage-specific efficacy and safety profiles of lecanemab and donanemab in early AD, focusing on patients with mild cognitive impairment (MCI) and those with mild dementia.

Subgroups were defined as follows: in TRAILBLAZER-ALZ 2, participants were categorized as MCI (Mini-Mental State Examination [MMSE] ≥27) and mild AD (MMSE 20–26), whereas in Clarity AD, participants were classified as MCI due to AD and mild dementia due to AD. Published results and supplementary data from both trials were reviewed. In this summary, these categories are harmonized and presented as MCI and mild dementia. Subgroup data were extracted with a primary focus on Clinical Dementia Rating-Sum of Boxes (CDR-SB) (the primary outcome in Clarity AD and a secondary outcome in TRAILBLAZER-ALZ 2) and Integrated Alzheimer's Disease Rating Scale (iADRS) (the primary outcome in TRAILBLAZER-ALZ 2), with additional review of Alzheimer's Disease Assessment Scale–Cognitive Subscale and activities of daily living measures where available. All comparisons presented herein are indirect, cross-trial comparisons based on publicly available subgroup data. Numerical contrasts are illustrative rather than inferential, given differences in trial design, eligibility criteria, baseline characteristics, estimand definitions, discontinuation rules, and outcome implementation.

Overall, both antibodies slowed clinical decline by approximately 20%–35% versus placebo over 18 months (76 weeks in TRAILBLAZER-ALZ 2). In the MCI subgroup, lecanemab showed a between-group difference of ΔCDR-SB=−0.35 (approximately 28% slowing), while donanemab showed a numerically similar effect (ΔCDR-SB=−0.29), with a corresponding change in iADRS (+2.14). In the mild dementia subgroup, lecanemab showed a between-group difference of ΔCDR-SB=−0.62 (approximately 27% slowing), although this effect was not statistically significant, whereas donanemab demonstrated a numerically comparable effect (ΔCDR-SB=−0.68) with iADRS (+2.25) (**Table 1**).[1,2] Mechanistically, lecanemab binds to soluble Aβ protofibrils, targeting early toxic aggregates involved in synaptic dysfunction,[3]

Table 1. Stage-specific clinical efficacy of lecanemab and donanemab in early AD

Stage (baseline)	Treatment (trial)	Treated (No.)	Outcome difference vs. placebo	% slowing vs. placebo
MCI	Lecanemab (Clarity AD)	528	ΔCDR-SB=−0.35	28%
	Donanemab (TRAILBLAZER-ALZ 2)	146	ΔCDR-SB=−0.29; ΔiADRS=+2.14	30.4%; 39.3%
Mild dementia	Lecanemab	331	ΔCDR-SB=−0.62	27%
	Donanemab	713	ΔCDR-SB=−0.68; ΔiADRS=+2.25	32.5%; 19.2%

Values shown represent published subgroup results and are presented for descriptive cross-trial context only.
Both studies targeted patients with early symptomatic AD, including those at the MCI and mild dementia stages. All changes in CDR-SB and iADRS reflect the 18-month (Clarity AD) or 76-week (~18-month; TRAILBLAZER-ALZ 2) core treatment periods. % slowing values are derived from published trial results (see References).
Treated (No.) indicates the number of participants receiving active treatment in each baseline stage subgroup.
AD: Alzheimer's disease, MCI: mild cognitive impairment, CDR-SB: Clinical Dementia Rating-Sum of Boxes, iADRS: Integrated Alzheimer's Disease Rating Scale.

which may explain its consistent efficacy across early disease stages. In contrast, donanemab binds to pyroglutamate-modified Aβ in fibrillar plaques,[4] enabling rapid plaque clearance, which may influence its clinical profile, particularly in biologically favorable subgroups. Interpretation of stage-specific suitability should consider not only efficacy magnitude but also safety profiles and treatment durability.

Regarding safety, amyloid-related imaging abnormalities with edema or effusion (ARIA-E) were observed in 12.6% of lecanemab-treated patients and in 24% of those receiving donanemab.[1,2] Symptomatic ARIA-E occurred in 2.8% of lecanemab recipients and 6.1% with donanemab. In addition to ARIA-E, amyloid-related imaging abnormalities with hemosiderin deposition (ARIA-H) were more frequent with donanemab (31.4%) than with lecanemab (17.3%), reflecting a higher incidence of microhemorrhagic events. Collectively, the overall incidence of amyloid-related imaging abnormalities was higher with donanemab, reflecting its more aggressive plaque-clearing profile. Notably, three ARIA-related deaths were reported in the donanemab arm, while no treatment-related deaths occurred in the Clarity AD trial. However, readers should be aware that criteria for adjudicating 'treatment-related' deaths may not have been identical across the two trials, and this comparison should not be taken as a direct or inferential contrast without accounting for these methodological differences. The higher overall ARIA incidence observed with donanemab may be related to its more aggressive plaque-clearing profile, although this relationship does not imply direct causality. Prior work has suggested that vascular amyloid clearance may be mechanistically linked to microhemorrhagic events.[5] Infusion-related reactions were more common with lecanemab (26.4% vs. 8.7%), but typically mild. These safety differences may guide therapeutic choices, particularly in apolipoprotein E (APOE) ε4 carriers, who are at higher ARIA risk. ARIA risk is higher in APOE ε4 carriers; for example, ARIA-E incidence in Clarity AD was markedly higher in APOE ε4 homozygotes (32.6%) than in noncarriers (5.4%), and ARIA-H incidence was also higher in APOE ε4 homozygotes (39.0%) than in noncarriers (11.9%). In TRAILBLAZER-ALZ 2, ARIA-E was higher in APOE ε4 homozygotes (40.6%) than in heterozygotes (22.8%) or noncarriers (15.7%).

Tau positron emission tomography (PET) imaging was a key differentiator: TRAILBLAZER-ALZ 2 required tau PET for enrollment, enabling stratified analysis based on tau pathology. Donanemab's most pronounced benefits were observed in participants with low tau, while those with high tau burden derived less benefit.[2] Clarity AD did not require tau PET for enrollment or primary analyses, although an optional tau PET substudy was conducted; lecanemab nonetheless showed consistent effects across clinical subgroups. According to publicly released data, lecanemab-treated patients with low baseline tau burden demonstrated sustained clinical benefit, with a substantial proportion showing no decline or improvement on CDR-SB and other cognitive and functional measures over extended

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follow-up.[6] Both trials also reported biomarker changes (including plasma phosphorylated tau species), supporting target engagement beyond amyloid removal.

An additional key distinction between the 2 trials is the dosing strategy. In TRAILBLAZER-ALZ 2, donanemab dosing was stopped after participants met predefined amyloid plaque clearance criteria, whereas in Clarity AD, lecanemab was administered as continuous treatment throughout the study period. This difference (limited-duration vs. continuous dosing) may have implications for long-term stage-specific treatment strategies, including monitoring burden, cumulative ARIA risk, and durability of clinical benefit. These differences in dosing regimen should also be considered when interpreting stage-specific treatment strategies.

Taken together, these findings support a stage-adapted, benefit–risk–based approach rather than superiority of one agent over the other. Both antibodies represent clinically validated disease-modifying therapies for early AD, each with distinct mechanistic profiles, safety considerations, and trial designs. Based on the available indirect cross-trial data, lecanemab showed relatively consistent effects across MCI and mild dementia subgroups and a lower ARIA burden. Donanemab might appear to demonstrate greater numerical benefit in mild dementia, particularly in biologically favorable subgroups with low tau burden.

However, in the absence of head-to-head comparative data, stage-specific suitability should be framed as a benefit-risk decision that accounts for efficacy magnitude, ARIA risk (including APOE e4 status), monitoring burden, and expected durability, rather than as a definitive clinical recommendation. Importantly, this letter provides an indirect cross-trial comparison based on publicly available subgroup data. Given differences in trial design, eligibility criteria, baseline characteristics, estimands/statistical models, discontinuation rules, and outcome implementation, all numerical contrasts should be considered illustrative rather than inferential. Definitive guidance on stage-specific treatment selection will require direct head-to-head comparative data.

In conclusion, lecanemab and donanemab represent the first wave of clinically validated disease-modifying therapies for early AD. Their stage-specific efficacy and safety profiles highlight the promise of precision medicine in Alzheimer's care, supporting treatment personalization based on disease stage, pathology, and patient characteristics. In addition, long-term findings from the Clarity AD open-label extension suggest sustained clinical benefit and a stable safety profile with continuous lecanemab treatment for up to ~4 years (36–48 months),[7] with no new safety signals and declining ARIA rates after the initial treatment period. Comparable long-term data for donanemab were not available in equivalent published form at the time of this summary. A balanced long-term comparison between the two agents will require additional follow-up data from the donanemab program.

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