

Continued or Time-limited Treatment Benefits of Anti-amyloid Monoclonal Antibodies in Early Alzheimer’s Disease

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INTRODUCTION

- The approved amyloid-β targeting antibodies lecanemab and donanemab have both been shown to clear amyloid plaque and slow clinical disease progression in early Alzheimer’s disease (AD), and lecanemab also clears insoluble protofibrils.
- Donanemab is intended to be stopped at plaque clearance, while lecanemab is recommended for continued dosing beyond plaque clearance, without monitoring amyloid PET scans
- Understanding the progression of disease under both scenarios is essential for informed clinical decision-making

METHODS

Using estimates from group-level published TRAILBLAZER-ALZ 2 data:

- Compare participants who cleared plaques by 12 months and stopped treatment (early completers) with matched placebo participants
- Matched placebo was created by adjusting overall placebo group estimates by the percentile difference in CDR-SB seen between overall active group and early treatment completers
- Additionally, the following group comparisons were made:
 - Participants who did not clear plaques by 12 months (continuers) to matched placebo
 - Overall treated population to matched placebo
- Evaluate the treatment benefit in CDR-SB from 0-12 months, and from 12-18 months
- How does the treatment effect observed at the beginning of the trial persist when treatment is discontinued?

Using estimates from group-level published Clarity AD data:

- Compare overall treated population to matched placebo participants
- Additionally, the following group comparisons were made:
 - Projected early completers group to matched placebo
 - Projected continuers group to matched placebo
- Evaluate the treatment benefit in CDR-SB from 0-12 months, and from 12-18 months
- Does the treatment effect observed at the beginning of the trial continue after 1 year of therapy?

DISCUSSION

These findings, limited by reliance on published group-level estimates and assumptions on subgroups, suggest that treatment benefit continues to accumulate after discontinuing donanemab at plaque clearance from 12-18 months, but potentially at a slower rate. This highlights the lasting impact of plaque clearance can have for patients. Continuous treatment with lecanemab (regardless of expected plaque clearance) appears to result in a larger and consistent accumulation of benefits over 18 months. This highlights the potential benefits that longer-term lecanemab treatment could have in delaying clinical progression in Alzheimer’s Disease.

RESULTS

Figure 1 shows the CDR-SB declines in two active subgroups: early completers, continuers and the overall active group, highlights the different clinical profiles within the subgroups.

Figure 2 represents the disease progression on CDR-SB of the early completers and their matched placebo in TRAILBLAZER-ALZ 2. The mapped *Placebo Trajectory*, represented by the green line, allows for an isolated comparison to the active arm, only after 12-month (treatment discontinuation). TRAILBLAZER-ALZ 2 early completers, when compared to the matched placebo group, continued to slow by 18% during the 6 months after stopping therapy (month 12 to 18).

Figure 3 illustrates the disease progression on CDR-SB in the Clarity AD study. Clarity AD subjects on therapy, when compared to the overall placebo population (mapped to 12-18 months), showed **29%** slowing over the last 6 months of treatment.

Figure 1. Active early completers in TB2 has different disease trajectory compared to the overall active group

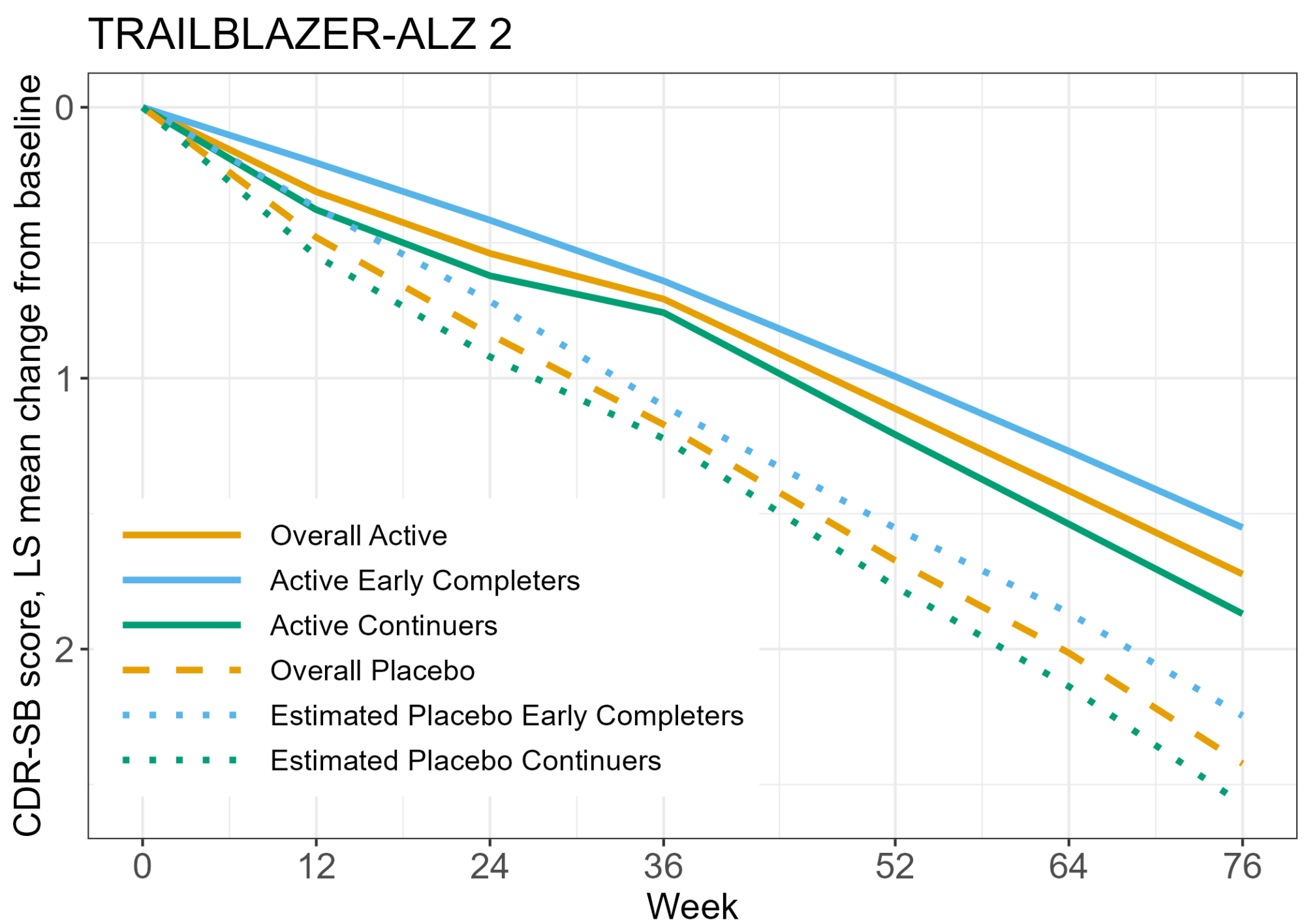


Figure 2
TRAILBLAZER-ALZ 2

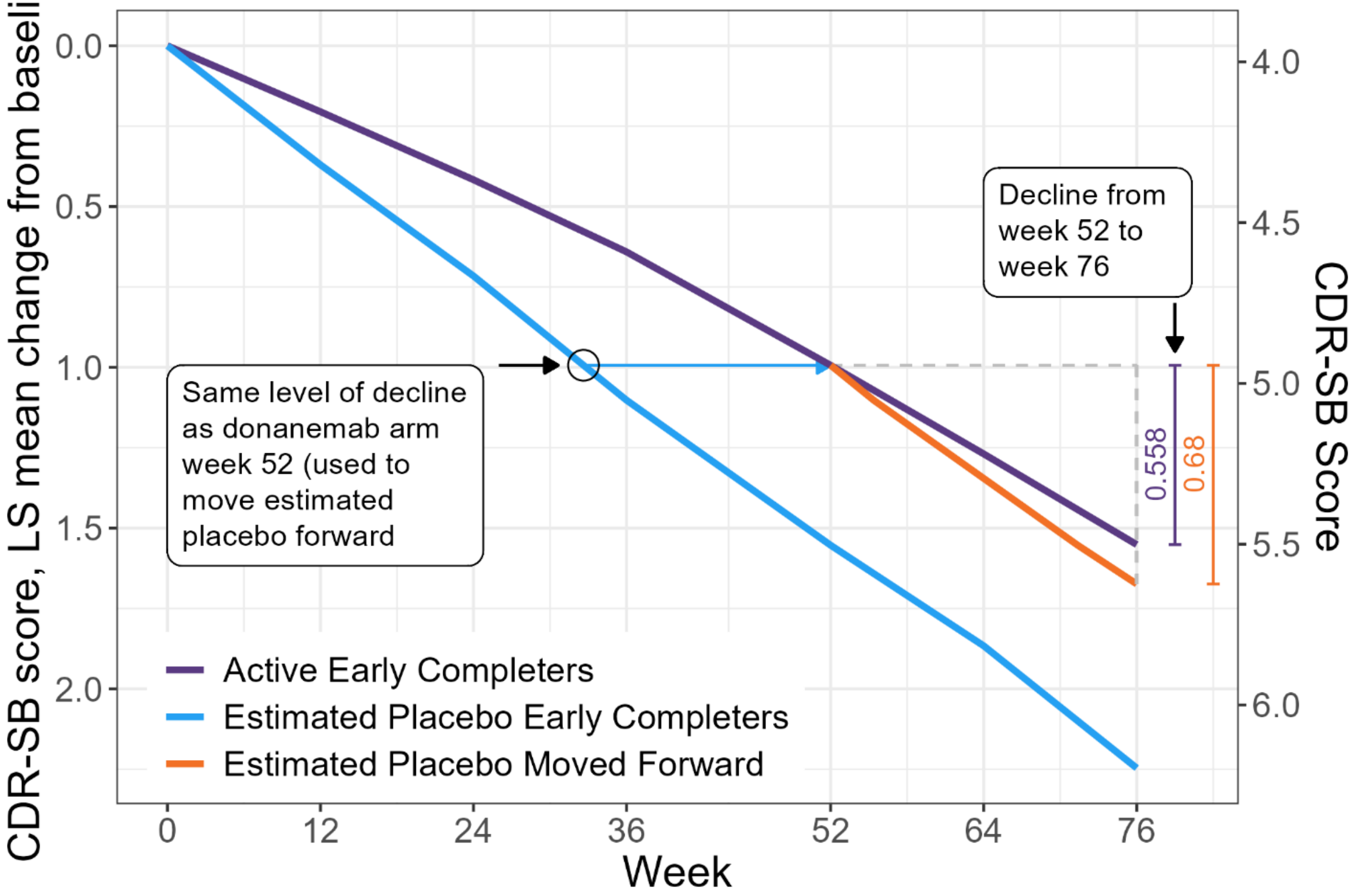


Figure 3
Clarity AD

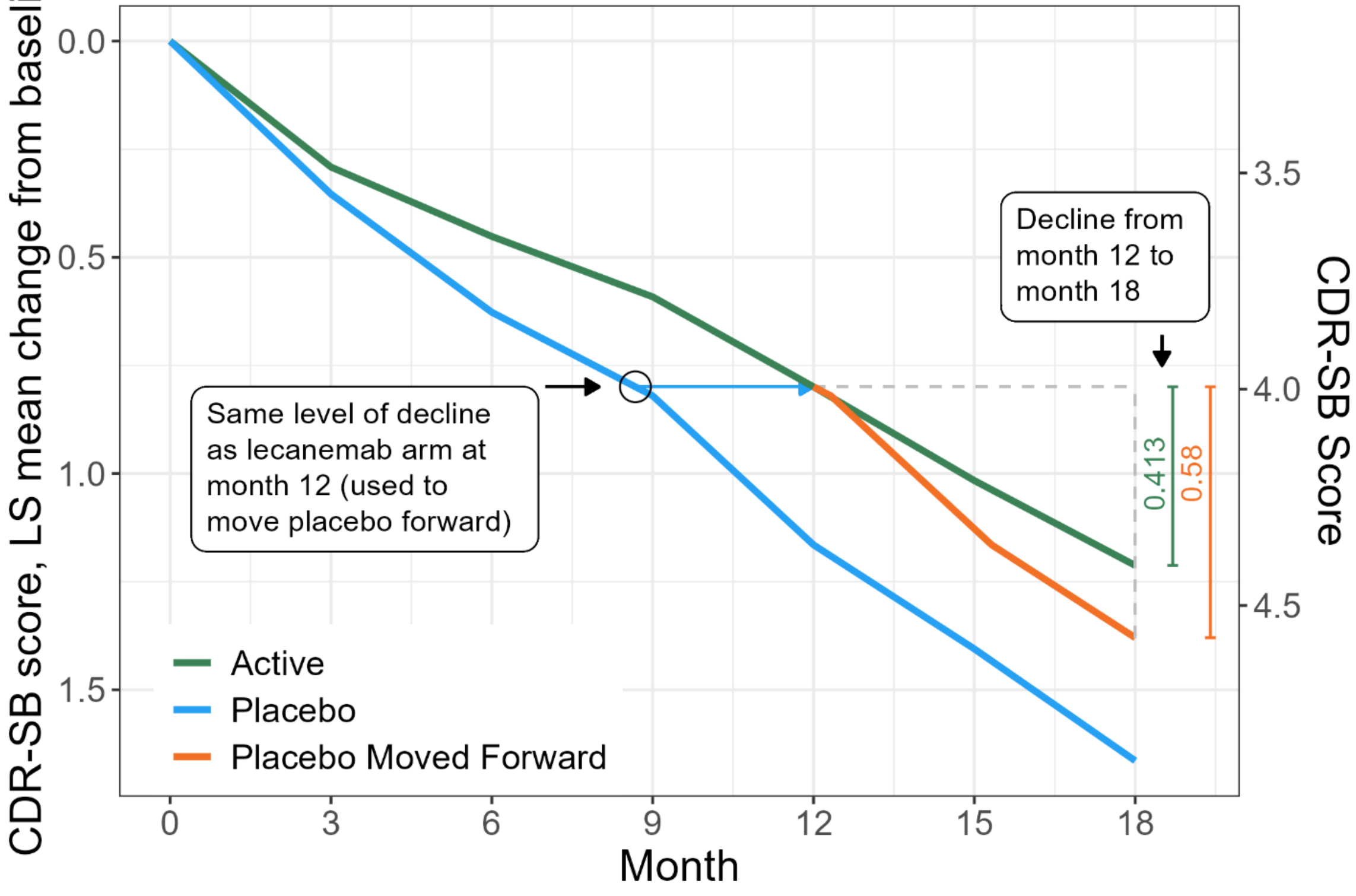


Table 1. Treatment effects in TRAILBLAZER-ALZ 2 and Clarity AD over time

Study	Timeframe	Subgroup	Treatment Difference* (95% CI)	Percent Slowing† (%)
TRAILBLAZER-ALZ 2	0-12 months	Overall population	-0.56 (-0.77, -0.35)	33.5
		Overall population	-0.12 (-0.36, 0.12)	16.0
	12-18 months	Early completers	-0.12 (-0.38, 0.14)	18.0
		Continuers	-0.13 (-0.46, 0.20)	16.1
Clarity AD	0-12 months	Overall population	-0.37 (-0.54, -0.19)	31.1
		Overall population	-0.17 (-0.38, 0.05)	28.8
	12-18 months	Projected early completers	-0.17 (-0.49, 0.15)	33.4
		Projected continuers	-0.19 (-0.49, 0.11)	28.9

*Treatment Difference: active group mean CDR-SB change score from baseline minus placebo group mean CDR-SB change score from baseline.

†Percent slowing is the treatment difference divided by the placebo mean change from baseline.

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.202313239
Dyck CH van, Swanson CJ, Aisen P, et al. Lecanemab in Early Alzheimer’s Disease. N Engl J Med. 2023;388(1):9-21. doi:10.1056/NEJMoa2212948

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