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Lecanemab in Early Alzheimer's Disease

TO THE EDITOR: In the phase 3 Clarity AD trial by van Dyck et al. (Jan. 5 issue),[1] the primary end point was the change from baseline to 18 months in the score on the Clinical Dementia Rating–Sum of Boxes (CDR-SB; scores range from 0 to 18, with higher scores indicating greater impairment). The minimal clinically relevant change in the CDR-SB score has been estimated to be 1 to 2 points.[2] At 18 months, the CDR-SB score had increased from baseline by 1.21 points with lecanemab and by 1.66 points with placebo, for a significant between-group difference of −0.45 points.[1] Therefore, participants with early Alzheimer's disease who had been assigned to receive either lecanemab or placebo had clinically meaningful declines in cognitive function over 18 months, whereas the between-group difference in the change in the CDR-SB score may not have been clinically meaningful.

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No potential conflict of interest relevant to this letter was reported.

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TO THE EDITOR: We are concerned about the possible lack of therapeutic efficacy among women in the trial by van Dyck and colleagues. Figure S1 in the Supplementary Appendix of their article (available at NEJM.org) shows that among men, the between-group difference (lecanemab vs. placebo) in the change from baseline to 18 months in the CDR-SB score was −0.73, which appears to be significant, whereas among women, the corresponding difference was only −0.20 (apparently not significant). This pattern was similar for all secondary outcomes (Figs. S2 to S4).

A point of scientific debate about the findings from the Clarity AD trial is in regard to their clinical significance at the individual level. The sex of the patients seems to be relevant in this respect. Since an analysis of such factors has been planned, the authors might clarify whether lecanemab is effective among women.

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Dr. Valenzuela reports being cofounder and chief executive officer of Skin2Neuron, which is developing a cell therapy for Alzheimer's disease. Dr. Pascual-Leone reports being cofounder and chief medical officer of Linus Health, which is developing digital technologies for diagnostic evaluation of brain health; being cofounder of TI Solutions, which is developing a device for noninvasive brain stimulation; and serving on the scientific advisory board for Neuroelectrics, Magstim, TetraNeuron, Skin2Neuron, MedRhythms, and Hearts Radiant. No other potential conflict of interest relevant to this letter was reported.

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TO THE EDITOR: The encouraging results of the Clarity AD trial of lecanemab could have been influenced by an effect of unblinding due to adverse events. More patients in the lecanemab group than in the placebo group had infusion-related reactions (26.4% vs. 7.4%) and amyloid-related imaging abnormalities with edema or effusions (ARIA-E) (12.6% vs. 1.7%). These dif-

ferences are of the same order of magnitude as the relative between-group difference in the change in the score on the CDR-SB, a subjective scale, of 27% in favor of lecanemab over placebo. The trial did not use more objective scales such as the Mini–Mental State Examination as a measure of cognition. Furthermore, the trajectory of mean scores on the 14-item cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-cog14) in the two trial groups during the last 3 months of the trial appeared to be parallel despite the marked decreases in brain amyloid burden and lowering of tau, phosphorylated tau 181, neurogranin, and glial fibrillary acidic protein levels. Conversely, no meaningful between-group differences in neurofilament light chain levels in cerebrospinal fluid and plasma were observed, a finding suggesting that treatment with lecanemab may not have reduced neuroaxonal damage.[1] These results highlight limitations of currently used biomarkers in predicting cognitive response in trials involving patients with Alzheimer's disease.

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No potential conflict of interest relevant to this letter was reported.

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TO THE EDITOR: In a phase 3 trial of lecanemab in the treatment of early Alzheimer's disease, van Dyck et al. identified a numerical benefit of lecanemab over placebo with respect to the change in the CDR-SB score at 18 months, with an adjusted mean difference of −0.45 points in favor of the drug (larger positive changes in CDR-SB scores indicate worse performance). However, the effect of the drug in a subgroup of apolipoprotein E (ApoE) ε4 homozygotes was +0.28 (Fig. S1B). This deleterious "score" is larger in magnitude than the beneficial adjusted mean score among all the women who received lecanemab (−0.20). Because ApoE ε4 homozygotes have more severe adverse reactions to antiamyloid infusions,[1,2] the subgroup of ApoE ε4 homozygous patients who finished the trial may have been selectively enriched with those who did not have adverse reactions to antiamyloid treatment. Because of potential functional unblinding and subsequent reporter or informant bias in CDR-SB scoring, the authors could provide ApoE genotype breakdowns for patients who left the trial and report the results of the CDR-SB cohort analysis with only the patients who had no adverse reactions to antiamyloid agents.

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No potential conflict of interest relevant to this letter was reported.

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THE AUTHORS REPLY: We disagree with Zeng et al. regarding the clinical meaningfulness of the between-group differences in the CDR-SB scores in our trial. The suggestion that the minimal clinically relevant change in the CDR-SB score is 1 to 2 points is, in our opinion, based on a methodologically flawed study.[1] In the estimate of the minimal clinically important difference in scores, the authors of that study mistakenly assumed that the clinician's assessment of meaningful decline in the National Alzheimer's Coordinating Center Uniform Data Set was made with respect to the participant's condition at the previous visit (and thus based on the same time interval as the change in CDR-SB score). In fact, this assessment of meaningful decline was made with respect to the participant's condition before the onset of symptoms, which renders these analyses uninterpretable. Moreover, the authors of that study have indicated that their findings should not be used for determining meaningful group-level differences in clinical trials.[2]

Valenzuela and Pascual-Leone correctly note that in several efficacy assessments, the point estimate among women was lower than that among men. However, the trial was not powered to evaluate individual subgroups. The subgroup

analyses indicate that lecanemab performed better than placebo with respect to all clinical, biomarker, and quality-of-life outcomes among women, findings that were consistent with the overall efficacy. Sex was not a significant covariate in the model. A treatment effect across all end points was observed among women as well as among men, although the effect was numerically smaller among women.

The sensitivity analyses (Table S2) address concerns raised by Pomara and Imbimbo about the effect of ARIA-E on the results. We disagree that the CDR-SB is a fully subjective scale, since it contains objective and direct assessments of the participants with respect to memory, orientation, judgment, and problem solving. It is a far more established outcome in studies involving patients with early Alzheimer's disease than the Mini–Mental State Examination. The ADAS-cog14 analysis shows that during the course of the 18-month study, the continuous decline in cognitive function was greater in the placebo group than in the lecanemab group, despite the relatively parallel decline in the final 3 months. With respect to the correspondents' concern about the use of current biomarkers, lecanemab showed effects across biomarkers of amyloid, tau, neurodegeneration, and gliosis that were consistent with biologic disease modification.

The concerns of Brenman about the efficacy of lecanemab in the subgroup of ApoE ε4 homozygous patients are similar to those about the efficacy of lecanemab among women and are addressed above. Moreover, although the changes in the CDR-SB score in this subgroup favored placebo over lecanemab, the changes in the ADAS-cog14 score, the score on the Alzheimer's Disease Cooperative Study–Activities of Daily Living Scale for Mild Cognitive Impairment (ADCS-MCI-ADL), the amyloid burden as measured by positron-emission tomography, plasma and cerebrospinal fluid biomarkers, and quality-of-life outcomes favored lecanemab over placebo. Brenman also mentions potential attrition bias and functional unblinding due to ARIA-E, which may differentially affect ApoE ε4 homozygotes. These issues are addressed for the full population by means of the primary modified intention-to-treat analytic approach, as well as by the sensitivity analyses that examined the effect of missing data and functional unblinding due to ARIA-E (Table S2). The trial was not powered to conduct sensitivity analyses within every subgroup.

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Since publication of their article, the authors report no further potential conflict of interest.

1. Andrews JS, Desai U, Kirson NY, Zichlin ML, Ball DE, Matthews BR. Disease severity and minimal clinically important differences in clinical outcome assessments for Alzheimer's disease clinical trials. Alzheimers Dement (N Y) 2019;5:354-63.
2. Petersen RC, Aisen PS, Andrews JS, et al. Expectations and clinical meaningfulness of randomized controlled trials. Alzheimers Dement 2023 February 7 (Epub ahead of print).

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