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Lecanemab in Early Alzheimer's Disease

C.H. van Dyck, C.J. Swanson, P. Aisen, R.J. Bateman, C. Chen, M. Gee, M. Kanekiyo, D. Li, L. Reyderman, S. Cohen, L. Froelich, S. Katayama, M. Sabbagh, B. Vellas, D. Watson, S. Dhadda, M. Irizarry, L.D. Kramer, and T. Iwatsubo

ABSTRACT

BACKGROUND

The accumulation of soluble and insoluble aggregated amyloid-beta (Aβ) may initiate or potentiate pathologic processes in Alzheimer's disease. Lecanemab, a humanized IgG1 monoclonal antibody that binds with high affinity to Aβ soluble protofibrils, is being tested in persons with early Alzheimer's disease.

METHODS

We conducted an 18-month, multicenter, double-blind, phase 3 trial involving persons 50 to 90 years of age with early Alzheimer's disease (mild cognitive impairment or mild dementia due to Alzheimer's disease) with evidence of amyloid on positron-emission tomography (PET) or by cerebrospinal fluid testing. Participants were randomly assigned in a 1:1 ratio to receive intravenous lecanemab (10 mg per kilogram of body weight every 2 weeks) or placebo. The primary end point was the 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). Key secondary end points were the change in amyloid burden on PET, the score on the 14-item cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-cog14; range, 0 to 90; higher scores indicate greater impairment), the Alzheimer's Disease Composite Score (ADCOMS; range, 0 to 1.97; higher scores indicate greater impairment), and the score on the Alzheimer's Disease Cooperative Study–Activities of Daily Living Scale for Mild Cognitive Impairment (ADCS-MCI-ADL; range, 0 to 53; lower scores indicate greater impairment).

RESULTS

A total of 1795 participants were enrolled, with 898 assigned to receive lecanemab and 897 to receive placebo. The mean CDR-SB score at baseline was approximately 3.2 in both groups. The adjusted least-squares mean change from baseline at 18 months was 1.21 with lecanemab and 1.66 with placebo (difference, −0.45; 95% confidence interval [CI], −0.67 to −0.23; P<0.001). In a substudy involving 698 participants, there were greater reductions in brain amyloid burden with lecanemab than with placebo (difference, −59.1 centiloids; 95% CI, −62.6 to −55.6). Other mean differences between the two groups in the change from baseline favoring lecanemab were as follows: for the ADAS-cog14 score, −1.44 (95% CI, −2.27 to −0.61; P<0.001); for the ADCOMS, −0.050 (95% CI, −0.074 to −0.027; P<0.001); and for the ADCS-MCI-ADL score, 2.0 (95% CI, 1.2 to 2.8; P<0.001). Lecanemab resulted in infusion-related reactions in 26.4% of the participants and amyloid-related imaging abnormalities with edema or effusions in 12.6%.

CONCLUSIONS

Lecanemab reduced markers of amyloid in early Alzheimer's disease and resulted in moderately less decline on measures of cognition and function than placebo at 18 months but was associated with adverse events. Longer trials are warranted to determine the efficacy and safety of lecanemab in early Alzheimer's disease. (Funded by Eisai and Biogen; Clarity AD ClinicalTrials.gov number, NCT03887455.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Dr. van Dyck can be contacted at christopher.vandyck@yale.edu or at the Alzheimer's Disease Research Unit, Division of Aging and Geriatric Psychiatry, Yale School of Medicine, 1 Church St., 8th Fl., New Haven, CT 06510.

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A Quick Take is available at NEJM.org

Current therapeutic agents for Alzheimer's disease–related dementia temporarily improve symptoms but do not alter the underlying disease course.[1,2] Some evidence suggests that amyloid removal slows the progression of disease.[3] One anti-amyloid antibody (aducanumab) has received accelerated approval from the Food and Drug Administration.

Lecanemab is a humanized monoclonal antibody that binds with high affinity to soluble amyloid-beta (Aβ) protofibrils, which have been shown to be more toxic to neurons than monomers or insoluble fibrils.[4-14] A phase 2b, dose-finding trial involving 854 participants with early Alzheimer's disease did not show a significant difference between lecanemab and placebo in a Bayesian analysis of 12-month change in a composite score (primary end point). However, analyses at 18 months showed dose- and time-dependent clearance of amyloid with lecanemab, and the drug was associated with less clinical decline on some measures than placebo. In that trial, intravenous administration of 10 mg of lecanemab per kilogram of body weight every 2 weeks was identified as an appropriate dose, with a 9.9% incidence (<3% symptomatic) of amyloid-related imaging abnormalities (ARIA) with edema or effusions (ARIA-E).[15] We conducted a phase 3 trial (Clarity AD) to determine the safety and efficacy of lecanemab in participants with early Alzheimer's disease.

Methods

Trial Design and Oversight

Clarity AD was an 18-month, multicenter, double-blind, placebo-controlled, parallel-group trial involving persons with early Alzheimer's disease. Eligible participants were randomly assigned in a 1:1 ratio to receive intravenous lecanemab (10 mg per kilogram every 2 weeks) or placebo. The randomization was stratified according to clinical subgroup (mild cognitive impairment due to Alzheimer's disease or mild Alzheimer's disease–related dementia on the basis of the criteria noted below), the presence or absence of concomitant approved medication for symptoms of Alzheimer's disease at baseline (e.g., acetylcholinesterase inhibitors, memantine, or both), apolipoprotein E (ApoE) ε4 carriers or noncarriers, and geographic region. During the trial, participants underwent serial blood testing for plasma biomarkers and could participate in three optional substudies that evaluated longitudinal changes in brain amyloid burden as measured by positron-emission tomography (PET), brain tau pathologic features as measured by PET, and cerebrospinal fluid (CSF) biomarkers of Alzheimer's disease.

The trial was conducted in accordance with International Council for Harmonisation guidelines and the ethical principles of the Declaration of Helsinki. The trial was approved by the institutional review board or independent ethics committee at each center, and all the participants provided written informed consent. The sponsor Eisai designed the trial and analyzed the data in collaboration with the academic authors, provided lecanemab and placebo, provided funding for medical writing, and aided in drafting the manuscript. The sponsor could not delay or interdict publication. The first, second, and sixteenth authors wrote the first draft of the manuscript, with professional medical writing assistance funded by Eisai, and all the authors contributed to subsequent drafts. Confidentiality agreements were in place between the sponsor and the authors and site investigators. Biogen provided partial funding for the trial.

An independent data and safety monitoring board consisting of experts in Alzheimer's disease and statistics reviewed unblinded safety data during the trial. An independent medical monitoring team, whose members were unaware of the trial-group assignments, reviewed ARIA, infusion-related reactions, and hypersensitivity reactions. Clinical assessment raters were unaware of the safety assessments and the trial-group assignments. All the authors vouch for the completeness and accuracy of the data, the fidelity of the trial to the protocol (available with the full text of this article at NEJM.org), and the full reporting of adverse events.

Eligibility Criteria

The trial included participants 50 to 90 years of age, with either mild cognitive impairment due to Alzheimer's disease or mild Alzheimer's disease–related dementia on the basis of National Institute on Aging–Alzheimer's Association criteria.[16,17] Amyloid positivity was determined by PET or CSF measurement of $A\beta_{1-42}$. All the participants had objective impairment in episodic memory as indicated by at least 1 standard deviation below the age-adjusted mean in the Wechsler Memory Scale IV–Logical Memory II.

END POINTS

The primary efficacy end point was the change in the score on the Clinical Dementia Rating (CDR)–Sum of Boxes (CDR-SB)[18] from baseline at 18 months. The CDR-SB score is a validated outcome measure used in clinical trials of Alzheimer's disease that is obtained by interviewing patients and their care partners and captures cognition and function. It assesses six domains that patients and caregivers identify as important (Memory, Orientation, Judgment and Problem Solving, Community Affairs, Home and Hobbies, and Personal Care). Scores for each domain range from 0 to 3, with higher scores indicating greater impairment. Total scores range from 0 to 18, with a score of 0.5 to 6 indicating early Alzheimer's disease.

Key secondary end points were the change from baseline at 18 months in the following: amyloid burden on PET as measured in centiloids (with either florbetaben, florbetapir, or flutemetamol tracers) in a substudy, the score on the 14-item cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-cog14; range, 0 to 90, with higher scores indicating greater impairment),[19] the Alzheimer's Disease Composite Score (ADCOMS; range, 0 to 1.97, with higher scores indicating greater impairment),[20] and the score on the Alzheimer's Disease Cooperative Study–Activities of Daily Living Scale for Mild Cognitive Impairment (ADCS-MCI-ADL; range, 0 to 53, with lower scores indicating greater impairment).[21] Biomarker assessments included CSF biomarkers ($A\beta_{1-40}$, $A\beta_{1-42}$, total tau, phosphorylated tau 181 [p-tau181], neurogranin, and neurofilament light chain [NfL]) and plasma biomarkers ($A\beta_{42/40}$ ratio, p-tau181, glial fibrillary acidic protein [GFAP], and NfL). Tau PET and volumetric magnetic resonance imaging (MRI) results have not been fully analyzed.

A prespecified exploratory and multiplicity-unadjusted analysis examined the time to worsening of the global CDR score (range, 0 to 3, with higher scores indicating greater impairment). This end point was defined as the time to the first increase of at least 0.5 points in the global CDR score on two consecutive visits.

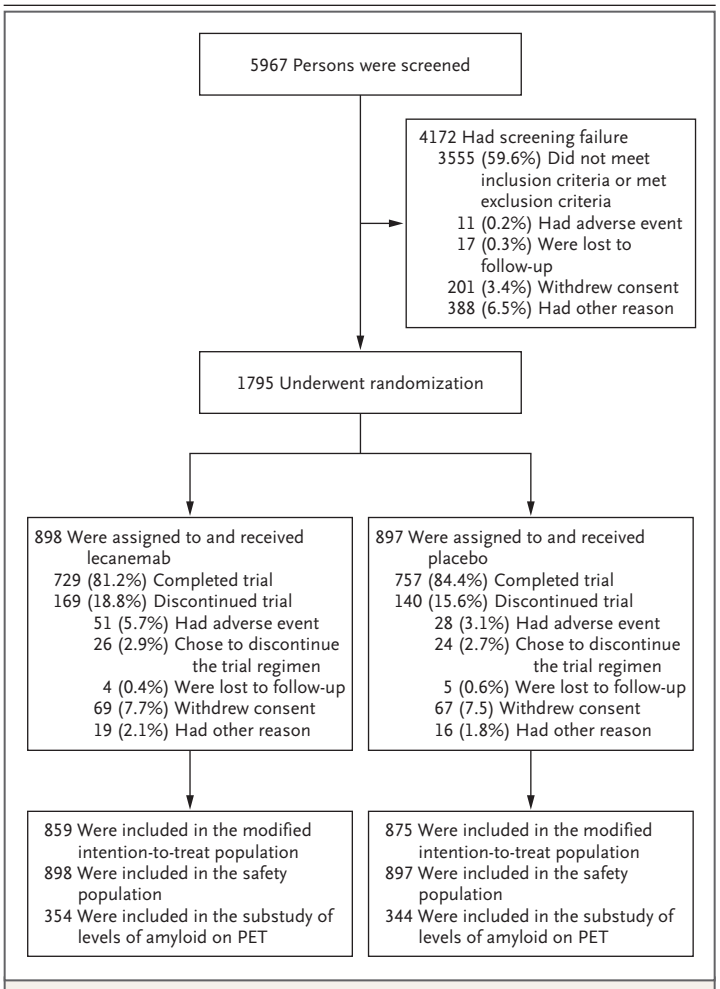


Figure 1. Screening, Randomization, and Follow-up.

Participants who completed visit 42 (at 18 months) are considered to have completed the trial. If the primary reason for trial discontinuation was missing, the participant was counted under "Other" for discontinuation reason. The modified intention-to-treat population included randomly assigned participants who received at least one dose of lecanemab or placebo and underwent assessment for the primary end point. PET denotes positron-emission tomography.

STATISTICAL ANALYSIS

The sample size for this trial was estimated on the basis of comparison of lecanemab and placebo with respect to the primary efficacy end point, the change from baseline at 18 months in the CDR-SB score. On the basis of data from the phase 2b trial of lecanemab,[15] the estimated standard deviation of the change from baseline at 18 months in the CDR-SB score with placebo was 2.031 points, and the estimated treatment difference between lecanemab and placebo in all the participants was 0.373 points. This estimation corresponds to 25% less decline in cognitive function with lecanemab than with placebo and is consistent with a clinically meaningful difference on the basis of the Alzheimer's disease literature, statistical principles, and agreements with regulatory authorities.[15,22-24] Therefore, under the assumption of an estimated 20%

dropout rate at 18 months in this trial, a total sample size of 1566 participants, including 783 participants receiving lecanemab and 783 participants receiving placebo, would provide the trial with 90% power to detect the treatment difference with the use of a two-sample t-test at a two-sided alpha level of 0.05. The sample size was increased by 200 to account for participants who missed three or more consecutive doses during the initial 6-month peak period of coro-

Table 1. Characteristics of the Participants at Baseline (Modified Intention-to-Treat Population).*

Characteristic	Lecanemab (N=859)	Placebo (N=875)
Age — yr	71.4±7.9	71.0±7.8
Sex — no. (%)		
Female	443 (51.6)	464 (53.0)
Male	416 (48.4)	411 (47.0)
Race — no. (%)†		
White	655 (76.3)	677 (77.4)
Black	20 (2.3)	24 (2.7)
Asian	147 (17.1)	148 (16.9)
Other or missing	37 (4.3)	26 (3.0)
Hispanic ethnic group — no. (%)†	107 (12.5)	108 (12.3)
Time since diagnosis — yr	1.41±1.51	1.34±1.54
Time since onset of symptoms — yr	4.13±2.35	4.15±2.53
Global CDR score — no. (%)‡		
0.5	694 (80.8)	706 (80.7)
1	165 (19.2)	169 (19.3)
Clinical subgroup — no. (%)		
Mild dementia due to Alzheimer's disease	331 (38.5)	331 (37.8)
Mild cognitive impairment due to Alzheimer's disease	528 (61.5)	544 (62.2)
ApoE ε4 status — no. (%)		
Noncarrier	267 (31.1)	275 (31.4)
Carrier	592 (68.9)	600 (68.6)
Heterozygotes	456 (53.1)	468 (53.5)
Homozygotes	136 (15.8)	132 (15.1)
Current use of medication for symptoms of Alzheimer's disease — no. (%)	447 (52.0)	468 (53.5)
CDR-SB score§		
Mean	3.17±1.34	3.22±1.34
Range	0.5 to 8.0	0.5 to 8.5
Amyloid burden on PET — centiloids¶		
Mean	77.92±44.84	75.03±41.82
Range	−16.6 to 213.2	−17.0 to 179.6
ADAS-cog14 score‖		
Mean	24.45±7.08	24.37±7.56
Range	4.7 to 47.7	5.0 to 60.7
ADCOMS**		
Mean	0.398±0.147	0.400±0.147
Range	0.08 to 0.94	0.07 to 0.91

Table 1. (Continued.)

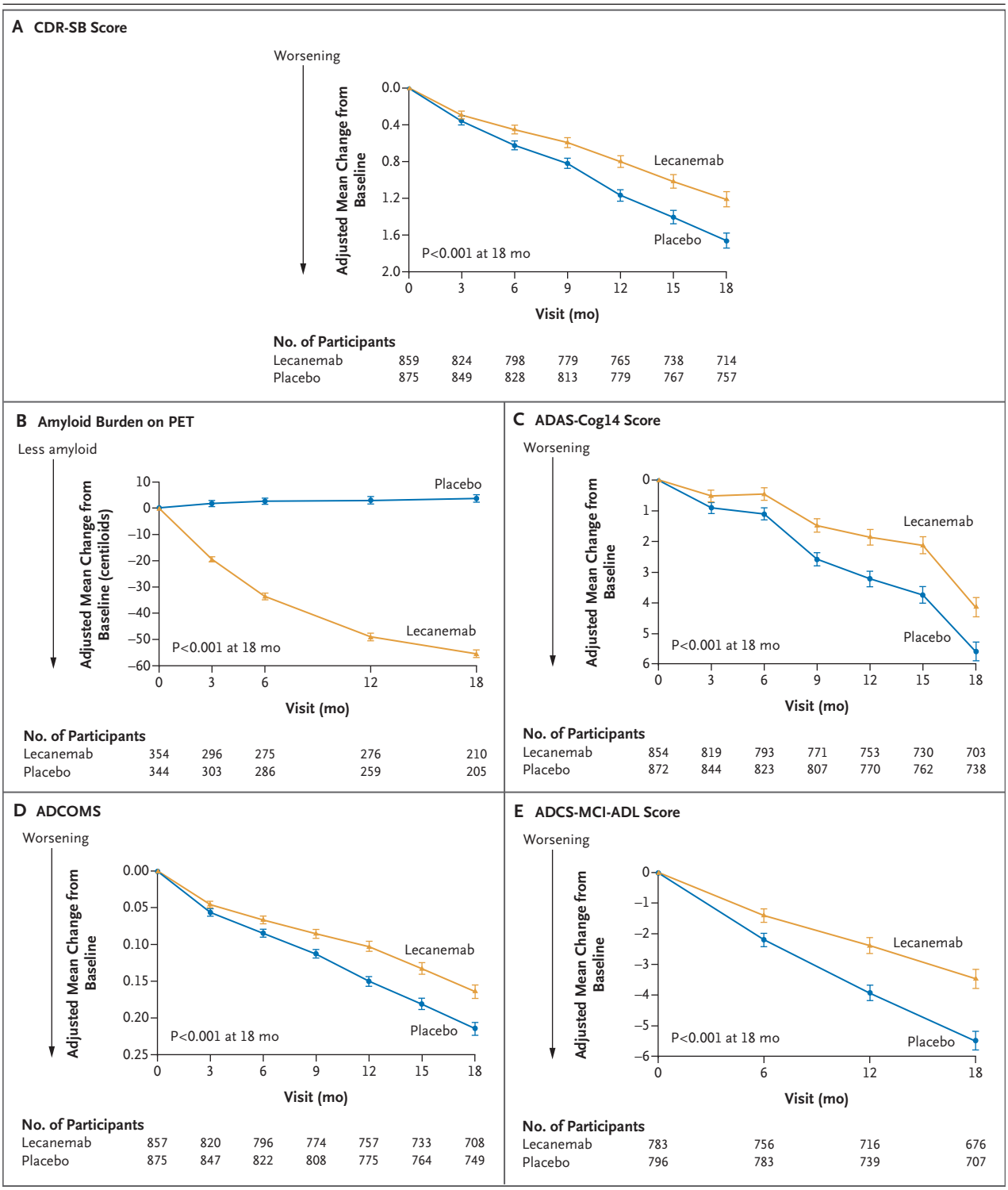
Characteristic	Lecanemab (N=859)	Placebo (N=875)
ADCS-MCI-ADL score††		
Mean	41.2±6.6	40.9±6.9
Range	13 to 53	12 to 53
MMSE score‡‡		
Mean	25.5±2.2	25.6±2.2
Range	22 to 30	22 to 30

* Plus–minus values are means ±SD. ApoE denotes apolipoprotein E.
† Race and ethnic group were determined by the participants.
‡ Global Clinical Dementia Rating (CDR) scores range from 0 to 3, with higher scores indicating greater impairment. A score of 0.5 is considered to be the threshold for Alzheimer's disease and was required for trial enrollment.
§ Scores on the CDR–Sum of Boxes (CDR-SB) range from 0 to 18, with higher scores indicating greater impairment.
¶ Values for amyloid burden on positron-emission tomography (PET) were for the PET substudy population.
‖ Scores on the 14-item cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-cog14) range from 0 to 90, with higher scores indicating greater impairment.
** Values for the Alzheimer's Disease Composite Score (ADCOMS) range from 0 to 1.97, with higher scores indicating greater impairment.
†† Scores on the Alzheimer's Disease Cooperative Study–Activities of Daily Living Scale for Mild Cognitive Impairment (ADCS-MCI-ADL) range from 0 to 53, with lower scores indicating greater impairment.
‡‡ Scores on the Mini–Mental State Examination (MMSE) range from 0 to 30, with lower scores indicating greater impairment.

navirus disease 2019 (Covid-19), in accordance with previous agreement with regulatory authorities. No interim analyses for futility or efficacy were planned or performed.

Efficacy analyses were performed in the modified intention-to-treat population, which was defined as the group of randomly assigned participants who received at least one dose of lecanemab or placebo and who had a baseline assessment and at least one postdose primary efficacy (CDR-SB) measurement. Sensitivity analyses across efficacy end points to assess the robustness of the primary analysis to missing data included rank analysis of covariance with imputation of missing values. Additional sensitivity analyses were performed to evaluate potential effects of functional unblinding due to ARIA and effects of missed doses due to Covid-19–related absences (see the Supplementary Appendix, available at NEJM.org). Safety was evaluated in the safety population, which was defined as the group of participants who received at least one dose of lecanemab or placebo. Safety evaluations included monitoring of adverse events, vital signs, physical examinations, clinical laboratory variables, and 12-lead electrocardiograms. Occurrences of ARIA were monitored throughout the trial by central reading of MRI performed at weeks 9, 13, 27, 53, and 79 as well as at the 3-month follow-up visit (week 91) for safety monitoring. In addition, the populations for the substudies of amyloid burden on PET, tau pathologic features on PET, and CSF biomarkers of Alzheimer's disease were the groups of participants who received at least one dose of lecanemab or placebo and who underwent a baseline PET or CSF evaluation and at least one postdose evaluation.

The primary analysis was performed without imputation of missing values. The primary analysis of the change from baseline at 18 months in the CDR-SB score was performed to compare lecanemab and placebo with the use of a mixed model for repeated measures that included the baseline CDR-SB score as a covariate, with trial group, visit, stratification variables (i.e., clinical subgroup, use of medication for symptoms of Alzheimer's disease at baseline [yes or no], ApoE ε4 carrier status [carriers or noncarriers], and geographic region [North America, Europe, and Asia–Pacific]), baseline CDR-SB score–by–visit interaction, and trial group–by–visit interaction as fixed effects. If the between-group difference in primary end-point results was significant, then key secondary end points were to be tested hierarchically in the following order: change from baseline at 18 months in amyloid burden



on PET as measured in centiloids in the subgroup tested and change from baseline at 18 months in the ADAS-cog14 score, change from baseline at 18 months in the ADCOMS, and change from baseline at 18 months in the ADCS-MCI-ADL score, all in the modified intention-to-treat population. Each test was performed at an alpha level of 0.05 (two-sided) and was to be

Figure 2 (facing page). Primary and Key Secondary End Points.

All panels except Panel B show results in the modified intention-to-treat population. Panel A shows the results for the primary end point, the score on the Clinical Dementia Rating–Sum of Boxes (CDR-SB). Scores for each of six domains range from 0 to 3, with higher scores indicating greater impairment. Total scores range from 0 to 18, with a score of 0.5 to 6 indicating early Alzheimer's disease. The adjusted mean changes from baseline, standard errors (indicated by I bars), and P value were derived with the use of a mixed model for repeated measures, with trial group, visit, trial group–by–visit interaction, clinical subgroup, use of medication for symptoms of Alzheimer's disease at baseline, ApoE ε4 carrier status, geographic region, and baseline value–by–visit interaction as fixed effects and baseline value as a covariate. Panels B through E show the results for the key secondary end points; values were calculated in the same manner as those for the primary end point. Panel B shows results for the change from baseline in amyloid burden on PET as measured in centiloids (with either florbetaben, florbetapir, or flutemetamol tracers) in a trial substudy. Panel C shows results for the change from baseline in the score on the 14-item cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-cog14; range, 0 to 90, with higher scores indicating greater impairment). Panel D shows results for the change from baseline in the Alzheimer's Disease Composite Score (ADCOMS; range, 0 to 1.97, with higher scores indicating greater impairment). Panel E shows results for the change from baseline in the score on the Alzheimer's Disease Cooperative Study–Activities of Daily Living Scale for Mild Cognitive Impairment (ADCS-MCI-ADL; range, 0 to 53, with lower scores indicating greater impairment).

performed only if the preceding test was significant at a two-sided level of 0.05. Additional details on the design and analysis methods are provided in the Supplementary Appendix and protocol.

RESULTS

PARTICIPANTS

A total of 5967 persons were screened and 1795 underwent randomization; 898 were assigned to receive lecanemab and 897 to receive placebo at 235 sites in North America, Europe, and Asia from March 2019 through March 2021. Of these participants, 729 (81.2%) in the lecanemab group and 757 (84.4%) in the placebo group completed the trial and had data available on the primary end point (Fig. 1). The modified intention-to-treat population included 1734 participants (859 in the lecanemab group and 875 in the placebo group), and the safety population included all 1795 randomly assigned participants. Enrollment in three longitudinal substudies included 698 participants in the substudy of amyloid burden on PET, 257 in the study of tau pathologic features on PET, and 281 in the substudy of CSF biomarkers of Alzheimer's disease. The baseline characteristics of the substudy groups were generally similar to those in the main analysis. This trial made efforts to enhance global enrollment of a diverse group of participants (20% non-White), including in the United States, where 6.1% and 28.1% of the 3638 screened participants and 4.5% and 22.5% of randomly assigned participants were Black and Hispanic, respectively. The characteristics of the participants at baseline were generally similar in the two trial groups (Table 1). These characteristics were similar to what has been observed in population studies involving persons with early Alzheimer's disease, although there was an underrepresentation of Black persons in the United States and an overrepresentation of Hispanic persons in the United States. The representativeness of the trial population is shown in Table S1 in the Supplementary Appendix.

END-POINT RESULTS

The mean CDR-SB score at baseline was approximately 3.2 in both the lecanemab and placebo groups, findings consistent with early Alzheimer's disease (score of 0.5 to 6). The adjusted mean change from baseline at 18 months in the CDR-SB score was 1.21 in the lecanemab group and 1.66 in the placebo group (difference, −0.45; 95% confidence interval [CI], −0.67 to −0.23; P<0.001) (Fig. 2A and Table 2).

In the substudy of amyloid burden on PET (a key secondary end point) involving 698 participants, the mean amyloid level at baseline was 77.92 centiloids in the lecanemab group and 75.03 centiloids in the placebo group. The adjusted mean change from baseline at 18 months was −55.48 centiloids in the lecanemab group and 3.64 centiloids in the placebo group (difference, −59.12 centiloids; 95% CI, −62.64 to −55.60; P<0.001) (Fig. 2B and Table 2). In the modified intention-to-treat population, the mean ADAS-cog14 scores at baseline were 24.45 in the lecanemab group and 24.37 in the placebo group. The adjusted mean change from baseline at 18 months in the ADAS-cog14 score was 4.14 in the lecanemab group and 5.58 in the placebo group (difference,

Table 2. Primary and Secondary End Points (Modified Intention-to-Treat Population).

End Point	Lecanemab (N=859)	Placebo (N=875)
Primary efficacy end point		
Change from baseline to 18 mo in the CDR-SB score		
No. of participants evaluated	859	875
Adjusted mean change	1.21	1.66
Adjusted mean difference vs. placebo (95% CI)	−0.45 (−0.67 to −0.23)	
P value vs. placebo	<0.001	
Secondary efficacy end points		
Change from baseline to 18 mo in amyloid burden on PET		
No. of participants evaluated	354	344
Adjusted mean change — centiloids	−55.48	3.64
Adjusted mean difference vs. placebo (95% CI) — centiloids	−59.12 (−62.64 to −55.60)	
P value vs. placebo	<0.001	
Change from baseline to 18 mo in the ADAS-cog14 score		
No. of participants evaluated	854	872
Adjusted mean change	4.14	5.58
Adjusted mean difference vs. placebo (95% CI)	−1.44 (−2.27 to −0.61)	
P value vs. placebo	<0.001	
Change from baseline to 18 mo in the ADCOMS		
No. of participants evaluated	857	875
Adjusted mean change	0.164	0.214
Adjusted mean difference vs. placebo (95% CI)	−0.050 (−0.074 to −0.027)	
P value vs. placebo	<0.001	
Change from baseline to 18 mo in the ADCS-MCI-ADL score		
No. of participants evaluated	783	796
Adjusted mean change	−3.5	−5.5
Adjusted mean difference vs. placebo (95% CI)	2.0 (1.2 to 2.8)	
P value vs. placebo	<0.001	

−1.44; 95% CI, −2.27 to −0.61; P<0.001) (Fig. 2C and Table 2). The mean ADCOMS in the modified intention-to-treat population at baseline was 0.398 in the lecanemab group and 0.400 in the placebo group. The adjusted mean change from baseline at 18 months in the ADCOMS was 0.164 in the lecanemab group and 0.214 in the placebo group (difference, −0.050; 95% CI, −0.074 to −0.027; P<0.001) (Fig. 2D and Table 2). In the modified intention-to-treat population, the mean ADCS-MCI-ADL scores at baseline were 41.2 for lecanemab and 40.9 for placebo. The adjusted mean change from baseline at 18 months in the ADCS-MCI-ADL score was −3.5 in the lecanemab group and −5.5 in the placebo group (difference, 2.0; 95% CI, 1.2 to 2.8; P<0.001) (Fig. 2E and Table 2).

For each of these assessments, separation of the trial groups was apparent by visual inspection of graphs at 3 months. However, no conclusions can be drawn because there was no prespecified plan for analysis that included adjustment of confidence intervals for multiple comparisons at any intermediate time point.

Sensitivity analyses of the CDR-SB score that evaluated the effect of Covid-19 (missed doses) and potential for bias from functional unblinding due to ARIA were generally consistent with the primary analysis (Table S2). Results were also consistent across key randomization strata, as well as

for other factors that affect Alzheimer's disease (Figs. S1 through S4). The exploratory subgroup analysis involving ApoE ε4 homozygotes (15% of the trial population) numerically favored lecanemab for the ADAS-cog14 and ADCS-MCI-ADL scores but not for the CDR-SB score and the ADCOMS. Results of prespecified analyses of end points involving CSF and plasma biomarkers showed numerical improvements for all assessments comparing lecanemab with placebo, with the exception of CSF NfL (Fig. S5). In a prespecified, multiplicity-unadjusted analysis of the time to worsening of the global CDR score, the hazard ratio for progression to the next stage of dementia (0.69) numerically favored lecanemab over placebo (Fig. S6).

SAFETY

Deaths occurred in 0.7% of the participants in the lecanemab group and 0.8% of those in the placebo group (Table 3). No deaths were considered by the investigators to be related to lecanemab or occurred with ARIA. Serious adverse events occurred in 14.0% of the participants in the lecanemab group and 11.3% of those in the placebo group. The most commonly reported serious adverse events were infusion-related reactions (in 1.2% of the participants in the lecanemab group and 0 participants in the placebo group), ARIA-E (in 0.8% and 0, respectively), atrial fibrillation (in 0.7% and 0.3%), syncope (in 0.7% and 0.1%), and angina pectoris (in 0.7% and 0). The overall incidence of adverse events was similar in the two groups (Table 3). Adverse events leading to discontinuation of the trial agent occurred in 6.9% of the participants in the lecanemab group and 2.9% of those in the placebo group. The most common adverse events (affecting >10% of the participants) in the lecanemab group were infusion-related reactions (26.4% with lecanemab and 7.4% with placebo); ARIA with cerebral microhemorrhages, cerebral macrohemorrhages, or superficial siderosis (ARIA-H; 17.3% with lecanemab and 9.0% with placebo); ARIA-E (12.6% with lecanemab and 1.7% with placebo); headache (11.1% with lecanemab and 8.1% with placebo); and falls (10.4% with lecanemab and 9.6% with placebo). Infusion-related reactions were largely mild to moderate (grade 1 or 2, 96%) and occurred with the first dose (75%). A total of 56% of the participants did not take preventative medications (i.e., nonsteroidal antiinflammatory drugs, antihistamines, or glucocorticoids) for infusion-related reactions. Of those who took preventative medications for subsequent doses, 63% did not have additional reactions.

Events of ARIA-E with lecanemab were mostly mild to moderate (91%) on the basis of central reading of imaging with the use of protocol definitions. These events were mostly asymptomatic (78%), occurred during the first 3 months of the treatment period (71%), and resolved within 4 months after detection (81%). A total of 2.8% of the participants in the lecanemab group had symptomatic ARIA-E; commonly reported symptoms were headache, visual disturbance, and confusion. The incidence of isolated ARIA-H (i.e., ARIA-H in participants who did not also have ARIA-E) was 8.9% in the lecanemab group and 7.8% in the placebo group. The incidence of isolated symptomatic ARIA-H was 0.7% in the lecanemab group and 0.2% in the placebo group. The most common symptom associated with isolated symptomatic ARIA-H was dizziness. Macrohemorrhage occurred in 5 of 898 participants (0.6%) in the lecanemab group and 1 of 897 participants (0.1%) in the placebo group. ARIA-H that occurred with ARIA-E tended to occur early (within 6 months). Isolated ARIA-H occurred throughout the trial. ARIA-E and ARIA-H were numerically less common among ApoE ε4 noncarriers than among carriers, with higher frequency among ApoE ε4 homozygotes than among ApoE ε4 heterozygotes (Table 3).

DISCUSSION

In this phase 3 trial, the change from baseline at 18 months in the CDR-SB score (primary end point) was less with lecanemab than with placebo, favoring lecanemab. Results for secondary clinical end points were in the same direction as those for the primary end point. Lecanemab has high selectivity for soluble aggregated species of Aβ as compared with monomeric amyloid, with moderate selectivity for fibrillar amyloid; this profile is considered to target the most toxic pathologic amyloid species.[4,7,8,13,14] After 18 months of treatment in the amyloid substudy, the mean amyloid level of 22.99 centiloids in the lecanemab group was below the threshold for amyloid positivity of approximately 30 centiloids, above which participants are considered to have elevated brain

Table 3. Adverse Events.*

Event	Lecanemab (N=898)	Placebo (N=897)
Overall — no. (%)		
Any adverse event	798 (88.9)	735 (81.9)
Adverse event related to lecanemab or placebo†	401 (44.7)	197 (22.0)
Serious adverse event	126 (14.0)	101 (11.3)
Death	6 (0.7)	7 (0.8)
Adverse event leading to discontinuation of the trial agent	62 (6.9)	26 (2.9)
Adverse event that occurred in ≥5% of participants in either group		
Infusion-related reaction	237 (26.4)	66 (7.4)
ARIA with microhemorrhages or hemosiderin deposits	126 (14.0)	69 (7.7)
ARIA-E	113 (12.6)	15 (1.7)
Headache	100 (11.1)	73 (8.1)
Fall	93 (10.4)	86 (9.6)
Urinary tract infection	78 (8.7)	82 (9.1)
Covid-19	64 (7.1)	60 (6.7)
Back pain	60 (6.7)	52 (5.8)
Arthralgia	53 (5.9)	62 (6.9)
Superficial siderosis of central nervous system	50 (5.6)	22 (2.5)
Dizziness	49 (5.5)	46 (5.1)
Diarrhea	48 (5.3)	58 (6.5)
Anxiety	45 (5.0)	38 (4.2)
ARIA‡		
ARIA-E — no. (%)	113 (12.6)	15 (1.7)
Symptomatic ARIA-E — no. (%)§	25 (2.8)	0
ApoE ε4 noncarrier — no./total no. (%)	4/278 (1.4)	0/286
ApoE ε4 carrier — no./total no. (%)	21/620 (3.4)	0/611
ApoE ε4 heterozygote	8/479 (1.7)	0/478
ApoE ε4 homozygote	13/141 (9.2)	0/133
ARIA-E according to ApoE ε4 genotype — no./total no. (%)		
ApoE ε4 noncarrier	15/278 (5.4)	1/286 (0.3)
ApoE ε4 carrier	98/620 (15.8)	14/611 (2.3)
ApoE ε4 heterozygote	52/479 (10.9)	9/478 (1.9)
ApoE ε4 homozygote	46/141 (32.6)	5/133 (3.8)
ARIA-H — no. (%)	155 (17.3)	81 (9.0)
Microhemorrhage	126 (14.0)	68 (7.6)
Superficial siderosis	50 (5.6)	21 (2.3)
Macrohemorrhage	5 (0.6)	1 (0.1)
Symptomatic ARIA-H§	6 (0.7)	2 (0.2)
Isolated ARIA-H: no concurrent ARIA-E	80 (8.9)	70 (7.8)

Table 3. (Continued.)

Event	Lecanemab (N=898)	Placebo (N=897)
ARIA-H according to ApoE ε4 genotype — no./total no. (%)		
ApoE ε4 noncarrier	33/278 (11.9)	12/286 (4.2)
ApoE ε4 carrier	122/620 (19.7)	69/611 (11.3)
ApoE ε4 heterozygote	67/479 (14.0)	41/478 (8.6)
ApoE ε4 homozygote	55/141 (39.0)	28/133 (21.1)
ARIA-E or ARIA-H — no. (%)	193 (21.5)	85 (9.5)
Concurrent ARIA-E and ARIA-H — no. (%)	74 (8.2)	9 (1.0)

* ARIA denotes amyloid-related imaging abnormalities, ARIA-E ARIA with edema or effusions, ARIA-H ARIA with hemosiderin deposits, and Covid-19 coronavirus disease 2019.
† The relatedness of adverse events to lecanemab or placebo was determined by the investigators.
‡ ARIA events were based on central review of MRI studies and include events that occurred after the double-blind intervention period.
§ Symptomatic ARIA-H concurrent with ARIA-E were included under ARIA-E.

amyloid levels.[25] In the CSF substudy and in plasma analyses involving the overall population, markers of amyloid, tau, neurodegeneration, and neuroinflammation (plasma GFAP) were reduced to a greater extent with lecanemab than with placebo, with the exception of NfL, which is less sensitive to neurodegeneration than the other markers and has a slower time course for change than the others.

A definition of clinically meaningful effects in the primary end point of the CDR-SB score has not been established; however, this trial exceeded the prospectively defined target, with an estimated treatment difference of 0.373 points on a scale range of 18, a baseline value of 3.2, and early Alzheimer's disease typically characterized by a score of 0.5 to 6. In a prespecified exploratory and multiplicity-unadjusted analysis of the time to worsening (increase) of the global CDR score of at least 0.5 points on two consecutive visits, the hazard ratio for progression to the next stage of dementia numerically favored lecanemab over placebo. An open-label extension study of Clarity AD is ongoing to provide additional safety and efficacy data beyond 18 months.

In the lecanemab group, the incidence of ARIA-E was 12.6%, and the incidence of ARIA-H was 17.3%. These incidences compare with 9.9% and 10.7%, respectively, in the phase 2b trial of lecanemab, in which ApoE ε4 carriers were underrepresented in the group that received 10 mg per kilogram every 2 weeks.[15] The incidence of ARIA, including symptomatic ARIA, was numerically lower than in similar clinical trials, but differences in the drugs used and in trial design do not allow direct comparisons.[26,27] ARIA-E generally occurred in the first 3 months, was mild and asymptomatic, did not lead to discontinuation of lecanemab or placebo if mild, and resolved within 4 months. The incidences of both overall and symptomatic ARIA-E were highest among ApoE ε4 homozygotes.

Among the limitations of this trial is that it includes data for only 18 months of treatment; an open-label extension study is ongoing. The Clarity AD trial was conducted during the Covid-19 pandemic and encountered obstacles including missed doses, delayed assessments, and intercurrent illnesses. The dropout rate was 17.2%, and a sensitivity analysis that evaluated the effect of missed doses was consistent with the primary end-point analysis. An additional potential limitation was the use of modified intention-to-treat analysis without imputation of missing values. However, a sensitivity analysis that was conducted with the use of a standard intention-to-treat population with imputation yielded similar results. Finally, occurrences of ARIA may have

caused participants and investigators to be aware of the trial-group assignments. We attempted to minimize this bias by making clinical raters unaware of the safety assessments and the trial-group assignments, and sensitivity analyses that were performed to examine the effect of ARIA on clinical outcomes showed that ARIA had no effect on the results. Additional trials of lecanemab include a 5-year phase 2 long-term extension trial (ClinicalTrials.gov number, NCT01767311) and a 4-year phase 3 long-term extension trial (NCT03887455) in early Alzheimer's disease, the 4-year AHEAD 3-45 trial (NCT04468659) in preclinical Alzheimer's disease, and the 4-year DIAN-TU (Dominantly Inherited Alzheimer Network Trials Unit) Next Generation trial (NCT05269394) in dominantly inherited Alzheimer's disease.

In persons with early Alzheimer's disease, lecanemab reduced brain amyloid levels and was associated with moderately less decline on clinical measures of cognition and function than placebo at 18 months but was associated with adverse events. Longer trials are warranted to determine the efficacy and safety of lecanemab in early Alzheimer's disease.

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A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

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APPENDIX

The authors' full names and academic degrees are as follows: Christopher H. van Dyck, M.D., Chad J. Swanson, Ph.D., Paul Aisen, M.D., Randall J. Bateman, M.D., Christopher Chen, B.M., B.Ch., Michelle Gee, Ph.D., Michio Kanekiyo, M.S., David Li, Ph.D., Larisa Reyderman, Ph.D., Sharon Cohen, M.D., Lutz Froelich, M.D., Ph.D., Sadao Katayama, M.D., Marwan Sabbagh, M.D., Bruno Vellas, M.D., David Watson, Psy.D., Shobha Dhadda, Ph.D., Michael Irizarry, M.D., Lynn D. Kramer, M.D., and Takeshi Iwatsubo, M.D.

The authors' affiliations are as follows: the Alzheimer's Disease Research Unit, Yale School of Medicine, New Haven, CT (C.H.D.); Eisai, Nutley, NJ (C.J.S., M.K., D.L., L.R., S.D., M.I., L.D.K.); the Alzheimer's Therapeutic Research Institute, University of Southern California, San Diego (P.A.); Washington University School of Medicine in St. Louis, St. Louis (R.B.); the Memory, Aging, and Cognition Center, Department of Pharmacology, Yong Loo Lin School of Medicine, National University of Singapore, Singapore (C.C.); Eisai, Hatfield, United Kingdom (M.G.); Toronto Memory Program, Toronto (S.C.); Medical Faculty Mannheim, University of Heidelberg, Central Institute of Mental Health, Mannheim, Germany (L.F.); Katayama Medical Clinic, Okayama (S.K.), and the Department of Neuropathology, Graduate School of Medicine, University of Tokyo, and the National Center of Neurology and Psychiatry, Tokyo (T.I.) — all in Japan; Barrow Neurological Institute, Phoenix, AZ (M.S.); Toulouse Gerontopole University Hospital, Université Paul Sabatier, INSERM Unité 1295, Toulouse, France (B.V.); and Alzheimer's Research and Treatment Center, Wellington, FL (D.W.).

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