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Donanemab in Early Alzheimer's Disease

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ABSTRACT

BACKGROUND

A hallmark of Alzheimer's disease is the accumulation of amyloid-β (Aβ) peptide. Donanemab, an antibody that targets a modified form of deposited Aβ, is being investigated for the treatment of early Alzheimer's disease.

METHODS

We conducted a phase 2 trial of donanemab in patients with early symptomatic Alzheimer's disease who had tau and amyloid deposition on positron-emission tomography (PET). Patients were randomly assigned in a 1:1 ratio to receive donanemab (700 mg for the first three doses and 1400 mg thereafter) or placebo intravenously every 4 weeks for up to 72 weeks. The primary outcome was the change from baseline in the score on the Integrated Alzheimer's Disease Rating Scale (iADRS; range, 0 to 144, with lower scores indicating greater cognitive and functional impairment) at 76 weeks. Secondary outcomes included the change in scores on the Clinical Dementia Rating Scale–Sum of Boxes (CDR-SB), the 13-item cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-Cog$_{13}$), the Alzheimer's Disease Cooperative Study–Instrumental Activities of Daily Living Inventory (ADCS-iADL), and the Mini–Mental State Examination (MMSE), as well as the change in the amyloid and tau burden on PET.

RESULTS

A total of 257 patients were enrolled; 131 were assigned to receive donanemab and 126 to receive placebo. The baseline iADRS score was 106 in both groups. The change from baseline in the iADRS score at 76 weeks was −6.86 with donanemab and −10.06 with placebo (difference, 3.20; 95% confidence interval, 0.12 to 6.27; P=0.04). The results for most secondary outcomes showed no substantial difference. At 76 weeks, the reductions in the amyloid plaque level and the global tau load were 85.06 centiloids and 0.01 greater, respectively, with donanemab than with placebo. Amyloid-related cerebral edema or effusions (mostly asymptomatic) occurred with donanemab.

CONCLUSIONS

In patients with early Alzheimer's disease, donanemab resulted in a better composite score for cognition and for the ability to perform activities of daily living than placebo at 76 weeks, although results for secondary outcomes were mixed. Longer and larger trials are necessary to study the efficacy and safety of donanemab in Alzheimer's disease. (Funded by Eli Lilly; TRAILBLAZER-ALZ ClinicalTrials.gov number, NCT03367403.)

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Accumulation of amyloid-β (Aβ) peptide in the form of amyloid plaques in the brain is an early event in Alzheimer's disease that putatively leads to neurodegeneration with cognitive and functional impairment.[1-4] A role for amyloid plaques in disease progression is supported by studies of uncommon genetic variants that increase or decrease Aβ deposition.[5,6] The presence of amyloid plaques early in the disease increases the likelihood of progression from mild cognitive impairment to dementia.[7] Interventions aimed at removal of amyloid plaques are hypothesized to slow the clinical progression of Alzheimer's disease. A second neuropathological hallmark of Alzheimer's disease is the presence of intracellular neurofibrillary tangles that contain hyperphosphorylated tau protein. Current disease models suggest that Aβ triggers tau pathology, with a complex and synergistic interaction between Aβ and tau manifesting at later stages and leading to progression of Alzheimer's disease.[8]

Donanemab is a humanized IgG1 antibody directed at an N-terminal pyroglutamate Aβ epitope that is present only in established plaques.[9-11] It is specific for this epitope and shows no off-target binding to other Aβ species,[9] neurotransmitters, or their receptors and has no known symptomatic effect. In a phase 1a study involving patients with amyloid-positive prodromal-to-moderate Alzheimer's disease, the safety, pharmacokinetics, and pharmacodynamics of donanemab were assessed after the administration of multiple doses.[10,11] In a phase 1b study involving patients with amyloid-positive mild cognitive impairment or mild-to-moderate Alzheimer's disease with dementia, donanemab reduced the amyloid plaque level as measured by the uptake of ^{18}F-florbetapir tracer on positron-emission tomography (PET), even after a single dose.[12,13] We conducted a phase 2 trial to evaluate the safety and efficacy of donanemab in patients with early symptomatic Alzheimer's disease.[14]

METHODS

TRIAL OVERSIGHT

TRAILBLAZER-ALZ is a multicenter, randomized, double-blind, placebo-controlled phase 2 trial that assessed the safety, adverse events, and efficacy of donanemab in patients with early Alzheimer's disease. The trial was conducted across 56 sites in the United States and Canada in accordance with the protocol (available with the full text of this article at NEJM.org) and with the consensus ethics principles derived from international ethics guidelines, including the Declaration of Helsinki and the Council for International Organizations of Medical Sciences International Ethical Guidelines. Trial participants provided written informed consent. An independent external data monitoring committee held quarterly reviews of unblinded safety data.

The trial sponsor, Eli Lilly, designed and funded the trial, provided donanemab and placebo, analyzed the data, and provided professional writing assistance in drafting the manuscript. The authors vouch for the accuracy and completeness of the data, the fidelity of the trial to the protocol, and complete reporting of adverse events. Authors employed by the sponsor contributed to the design of the trial. An academic author and authors employed by the sponsor contributed to the collection and analysis of the data. The academic authors and authors employed by the sponsor contributed to the interpretation of the data. All the authors contributed to drafting or critical revision of the manuscript, as well as reviewed and approved versions of the manuscript to be submitted for publication. (Details regarding individual author contributions are provided in the Supplementary Appendix, available at NEJM.org.) The sponsor retained the right to review the manuscript for intellectual property purposes and to confirm the accuracy of all data and analyses. Confidentiality agreements were in place between the sponsor and the authors and site investigators.

ELIGIBILITY CRITERIA

The trial included patients 60 to 85 years of age who had early symptomatic Alzheimer's disease, defined as prodromal Alzheimer's disease (the symptomatic predementia phase of Alzheimer's disease in which mild cognitive impairment is apparent, as defined in the protocol) or mild Alzheimer's disease with dementia (in which symptoms are sufficiently severe to meet diagnostic criteria for dementia and Alzheimer's disease),[15] and had a Mini–Mental State Examination (MMSE) score of 20 to 28 (scores range from 0 to 30, with higher scores indicating better mental performance).[16] Screening procedures included the MMSE, PET with injection of

^{18}F-flortaucipir, magnetic resonance imaging (MRI), and then PET with injection of ^{18}F-florbetapir. The flortaucipir and florbetapir PET scans were reviewed at a centralized PET imaging facility for assessment of eligibility.

Patients were required to have flortaucipir PET scans with evidence of pathologic tau deposition but with quantitative tau levels below a specific upper threshold. The latter criterion was included to address the concern that antiamyloid treatments would have limited efficacy in advanced disease, as indicated by the presence of extensive tau pathology. Thus, flortaucipir PET scans were quantitatively evaluated for estimation of a tau standardized uptake value ratio (SUVR) according to published methods[17-19] and were visually evaluated for detection of a tau deposition pattern consistent with Alzheimer's disease.[20] Patients with an SUVR of more than 1.46 were considered to have a high tau level and were excluded from the trial. Patients with an SUVR of less than 1.10 or with a deposition pattern not consistent with Alzheimer's disease were considered to have an inadequate tau level and were excluded from the trial, except for patients with an SUVR of less than 1.10 but with a topographic deposition pattern consistent with advanced Alzheimer's disease, who were included.

In accordance with the protocol, patients were required to meet all eligibility criteria assessed at the first visit, except for undergoing MRI, before they underwent screening with florbetapir PET. The number of patients who were excluded from the trial because of screening failure is shown in Figure 1; information regarding the specific reasons for screening failure is provided in Table S1 in the Supplementary Appendix. The sequence of screening procedures and the flortaucipir PET criteria ensured that only a small percentage (0.9%) of patients in the population assessed for eligibility who met the flortaucipir PET criteria did not meet the florbetapir PET criterion (amyloid SUVR ≥1.17, equivalent to 37 centiloids).

INTERVENTIONS

Patients who met the eligibility criteria were randomly assigned in a 1:1 ratio to receive either donanemab (700 mg for the first three doses and 1400 mg thereafter) or placebo, administered intravenously every 4 weeks for up to 72 weeks. Randomization was stratified according to investigative site only. In participants who were treated with donanemab, if the amyloid plaque level as assessed by florbetapir PET (performed at 24 and 52 weeks) was 11 to less than 25 centiloids, indicating removal of amyloid plaques, the dose was lowered to 700 mg. If the amyloid plaque level was less than 11 centiloids on any one scan or was 11 to less than 25 centiloids on two consecutive scans, donanemab was switched to placebo. If amyloid-related imaging abnormalities with edema or effusions (ARIA-E) — defined as signal hyperintensities on fluid-attenuated inversion recovery MRI sequences due to parenchymal fluid accumulation or sulcal fluid effusion[21] — occurred with the first three doses of 700 mg, the dose was not increased. Final safety and efficacy assessments were performed at 76 weeks, 4 weeks after the last infusion.

Early versions of the protocol included a group assigned to receive donanemab in combination with LY3202626, an inhibitor of β-site amyloid precursor protein–cleaving enzyme 1 (BACE1). After the trial began, development of the BACE1 inhibitor was ceased because of a finding of futility in an ongoing phase 2 trial of the agent, and the combination-therapy group was discontinued.[22-24] The results presented here do not include data from the 15 participants who had been assigned to the combination-therapy group before its discontinuation.

SAFETY ASSESSMENTS

Safety assessments were performed by site investigators who were unaware of the trial group assignments. Safety outcomes included spontaneously reported adverse events, clinical laboratory test results, vital signs and body-weight measurements, and findings on 12-lead electrocardiography, physical and neurologic examinations, and MRI, as well as the score on the Columbia Suicide Severity Rating Scale.[25] Details regarding safety follow-up visits (which are ongoing) are provided in the protocol.

EFFICACY OUTCOMES

The primary outcome was the change from baseline to 76 weeks in the score on the Integrated Alzheimer's Disease Rating Scale (iADRS; scores range from 0 to 144, with lower scores indicating a greater cognitive deficit and greater impairment of the ability to perform activities of daily living).[26] The iADRS is a linear combina-

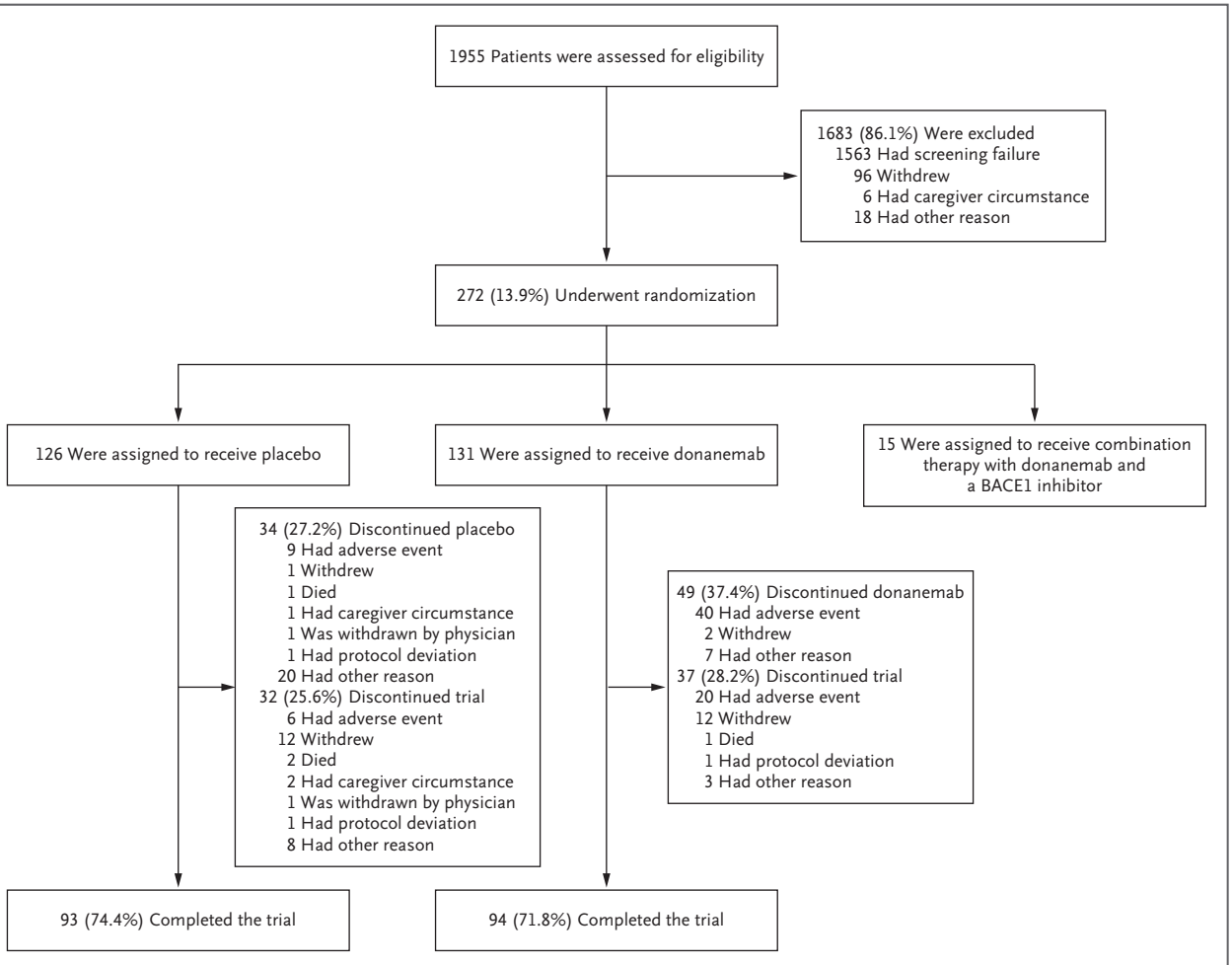


Figure 1. Enrollment, Randomization, and Trial Completion.

One participant was randomly assigned to the placebo group but discontinued the trial before receiving an infusion and was not included in the modified intention-to-treat population. The combination-therapy group was discontinued; details are provided in the protocol. Information regarding specific reasons for screening failure is provided in Table S1 in the Supplementary Appendix.

tion of its two components: the 13-item cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-Cog_{13}; scores range from 0 to 85, with higher scores indicating a greater deficit)[27] and the Alzheimer's Disease Cooperative Study–Instrumental Activities of Daily Living Inventory (ADCS-iADL; scores range from 0 to 59, with lower scores indicating greater impairment).[28,29] Because worse outcomes are indicated by higher scores on the ADAS-Cog_{13} and by lower scores on the ADCS-iADL, the ADAS-Cog_{13} score is multiplied by –1 in the calculation of the iADRS score, such that lower scores on the iADRS indicate greater impairment. The iADRS was developed to measure disease processes in Alzheimer's disease, and clinical trial data were used to identify items that performed best for that goal. The iADRS has been validated, and statistical properties of the composite performance have been described[30]; it has been used as a clinical outcome measure in previous phase 3 trials in Alzheimer's disease.[31,32]

The key secondary outcomes, subject to hierarchical statistical analysis, were the change from baseline in scores on the Clinical Dementia Rating Scale–Sum of Boxes (CDR-SB; scores range from 0 to 18, with higher scores indicating greater impairment),[33] the ADAS-Cog_{13}, the ADCS-iADL, and the MMSE. Details regarding other secondary outcomes, including the change

in the amyloid and tau burden as assessed by florbetapir PET and flortaucipir PET, respectively, and the change in results on volumetric MRI, are provided in the protocol. Assessment of the global tau load was performed with the use of a Tau^{IQ} algorithm, accounting for the spatiotemporal distribution of tau (details are provided in the Supplementary Appendix).

STATISTICAL ANALYSIS

We determined that enrollment of 250 participants (assigned in a 1:1 ratio to two trial groups, with 200 participants expected to complete the trial) would provide the trial with approximately 84% power to show a posterior probability of at least 0.6 that the active-treatment group will have at least 25% slower disease progression than the placebo group (as measured by the iADRS score). The power calculation was based on the assumption that there would be a mean decrease in the iADRS score of approximately 6 points in the donanemab group and 12 points in the placebo group (a 50% difference) over a period of 18 months, with a common standard deviation of 17.

Efficacy analyses were conducted on the basis of a modified intention-to-treat principle (unless otherwise specified), including data from participants who had a baseline and at least one postbaseline iADRS score. Pairwise tests of treatment effects were conducted at a two-sided alpha level of 0.05 (unless otherwise specified). Baseline characteristics were summarized according to trial group and overall, with the use of descriptive statistics for continuous and categorical measures.

The primary outcome was analyzed with the use of a mixed model for repeated measures (MMRM), with the change from baseline in the iADRS score at each scheduled postbaseline time point as the dependent variable. The model for the fixed effects included the following terms: baseline score, investigator, trial group, visit, interaction of trial group with visit, interaction of baseline score with visit, concomitant use of acetylcholinesterase inhibitors or memantine or both at baseline (yes or no), and age at baseline. The repeated measures across time were treated categorically. Secondary efficacy outcomes were assessed with the use of an MMRM (details are provided in the statistical analysis plan, included with the protocol). The graphical approach of Bretz and Maurer was used to provide control of the studywise type I error rate for the primary and key secondary outcomes at an alpha level of 0.05. If the results of the primary analysis were significant, the MMRM used for the primary analysis was to be used for analysis of the CDR-SB, ADAS-Cog$_{13}$, ADCS-iADL, and MMSE scores, with significance determined on the basis of a multiplicity graph of hypotheses. The analysis of the first secondary outcome in the graphical approach, the CDR-SB score, was conducted at the full alpha level, and the alpha levels of the remaining objectives were propagated as shown in the statistical analysis plan. Longitudinal clinical outcomes are provided with point estimates and standard error bars. For postbaseline categorical data, Fisher's exact test was used for trial group comparisons. For postbaseline continuous data collected at 76 weeks, an analysis of covariance model, with independent factors for trial group and age, was used. Each principal site investigator was responsible for selecting raters, who met training requirements, to administer the instruments at the site. Raters were unaware of the trial group assignments.

In addition, a Bayesian disease progression model was used to assess cognitive and functional decline as measured by the iADRS score in the donanemab group as compared with the placebo group across the 76 weeks of the trial, as prespecified in the protocol. The model assumes a proportional treatment effect relative to placebo and includes diffuse priors. A model used in a previous analysis of progression of autosomal dominant Alzheimer's disease was similar,[34] with the exception that in the current model, the prior distributions on the factors representing the decline in the placebo group were not forced to be monotonic. The analysis generates a posterior probability distribution of the disease progression ratio, defined as the proportional decline in the donanemab group as compared with the placebo group. A disease progression ratio of less than 1 favors donanemab. The 95% credible intervals and the posterior mean of the disease progression ratio were calculated from the disease progression ratio equation. The posterior probability of at least 25% slower disease progression in the active-treatment group than in the placebo group was prespecified as a positive outcome. The disease progression ratio was used to assess the relative cogni-

tive and functional decline as measured by the CDR-SB, ADAS-Cog$_{13}$, ADCS-iADL, and MMSE scores. The Bayesian disease progression models were not part of a prespecified multiplicity testing strategy for secondary outcomes, and no clinical conclusions can be drawn from these data. (Details regarding the Bayesian disease progression model are provided in the Supplementary Appendix.)

Safety outcomes (including adverse events, laboratory test results, vital signs, and findings on electrocardiography and MRI) were summarized with the use of descriptive statistics for continuous variables and frequencies for categorical variables during the intervention period (see the Supplementary Appendix).

A likelihood-based MMRM was used to handle missing data. The model coefficients were estimated simultaneously with the use of restricted maximum likelihood estimation that incorporated all observed data. When participants discontinued the trial early, efficacy or safety assessments may have been performed at visits for which data collection had not been scheduled.

RESULTS

TRIAL POPULATION

Of the 1955 patients assessed for eligibility, 257 were enrolled in the trial; 131 were assigned to receive donanemab and 126 to receive placebo (Fig. 1). One participant in the placebo group was not included in the modified intention-to-treat population. At the time of trial initiation, there were three groups, including a combination-therapy group assigned to receive donanemab and a BACE1 inhibitor. As described previously, the third group was discontinued early in the trial, and data from the 15 participants who had been assigned to that group were omitted from the final analysis (Fig. 1). Characteristics of the participants in that group are shown in Table S2. In the donanemab and placebo groups, the mean age was 75.0 and 75.4 years, respectively; 51.9% and 51.6% were women, 93.1% and 96.0% were White, and 72.5% and 74.2% were *APOE* ε4 carriers (Table 1). The mean baseline iADRS score was 106.2 in the donanemab group and 105.9 in the placebo group, the MMSE score 23.6 and 23.7, the CDR-SB score 3.6 and 3.4, the global tau load on flortaucipir PET 0.47 and 0.46, and the amyloid plaque level on florbetapir PET 107.6 and 101.1 centiloids (Table 1).

PRIMARY OUTCOME

The change from baseline in the iADRS score at 76 weeks was −6.86 in the donanemab group and −10.06 in the placebo group (difference, 3.20; 95% confidence interval [CI], 0.12 to 6.27; P=0.04) (Fig. 2A and Table S3); a smaller reduction indicates less cognitive and functional decline. The estimated percent change in the iADRS score in the donanemab group as compared with the placebo group at 76 weeks, analyzed with the MMRM, was similar to the Bayesian disease progression ratio over the entire 18-month period (Fig. 2C). On the basis of the Bayesian disease progression ratio, the posterior probability of at least 25% slower disease progression in the donanemab group than in the placebo group (as measured by the iADRS score) was calculated as 0.78.

SECONDARY OUTCOMES

Clinical Outcomes

The difference between the donanemab group and the placebo group in the change from baseline at 76 weeks was −0.36 (95% CI, −0.83 to 0.12) for the CDR-SB score, −1.86 (95% CI, −3.63 to −0.09) for the ADAS-Cog$_{13}$ score, 1.21 (95% CI, −0.77 to 3.20) for the ADCS-iADL score, and 0.64 (95% CI, −0.40 to 1.67) for the MMSE score (Fig. 2B and Table S3). Because the analysis of the first secondary outcome, the CDR-SB score, failed to show a significant difference between the two trial groups, the hierarchy failed and no definite conclusions can be drawn from data regarding the difference between groups in the change in the ADAS-Cog$_{13}$ score. The results for the ADCS-iADL and MMSE scores showed no substantial difference between groups.

Biomarker Outcomes

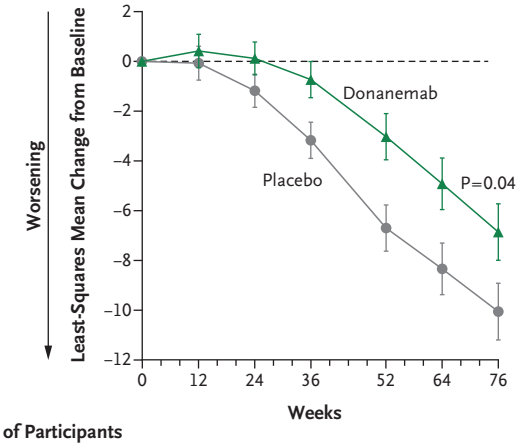
At 76 weeks, the reduction in the amyloid plaque level as assessed by florbetapir PET was 85.06 centiloids greater in the donanemab group than in the placebo group (−84.13 vs. 0.93 centiloids) (Fig. 3A). By 24 weeks, the reduction was 67.83 centiloids greater with donanemab than with placebo (−69.64 vs. −1.82 centiloids). The percentage of participants in the donanemab group who had amyloid-negative status (defined as an

Table 1. Characteristics of the Participants at Baseline.*

Variable	Donanemab (N=131)	Placebo (N=126)	Total (N=272)†
Female sex — no. (%)	68 (51.9)	65 (51.6)	145 (53.3)
Age — yr	75.0±5.6	75.4±5.4	75.2±5.5
Race or ethnic group — no. (%)‡			
Asian	1 (0.8)	2 (1.6)	3 (1.1)
Black	5 (3.8)	3 (2.4)	8 (2.9)
White	122 (93.1)	121 (96.0)	258 (94.9)
Other	3 (2.3)	0	3 (1.1)
Hispanic ethnic group — no. (%)‡	5 (3.8)	3 (2.4)	9 (3.3)
Education ≥13 yr — no. (%)	97 (74.0)	102 (81.0)	209 (76.8)
APOE ε4 carrier — no./total no. (%)	95/131 (72.5)	92/124 (74.2)	197/270 (73.0)
APOE genotype — no./total no. (%)			
ε2/ε3	1/131 (0.8)	1/124 (0.8)	2/270 (0.7)
ε2/ε4	2/131 (1.5)	2/124 (1.6)	4/270 (1.5)
ε3/ε3	35/131 (26.7)	31/124 (25.0)	71/270 (26.3)
ε3/ε4	68/131 (51.9)	62/124 (50.0)	137/270 (50.7)
ε4/ε4	25/131 (19.1)	28/124 (22.6)	56/270 (20.7)
Use of acetylcholinesterase inhibitor — no. (%)	78 (59.5)	74 (58.7)	162 (59.6)
Clinical outcomes — mean (range)			
iADRS score§	106.2±13.0 (60.0–130.0)	105.9±13.2 (67.0–139.0)	106.2±13.0 (60.0–139.0)
CDR-SB score¶	3.6±2.1 (0.5–11.0)	3.4±1.7 (0.5–8.0)	3.5±1.9 (0.5–11.0)
ADAS-Cog$_{13}$ score‖	27.6±7.7 (10.0–51.0)	27.5±7.6 (5.0–47.0)	27.6±7.6 (5.0–51.0)
ADCS-ADL score**	67.4±8.6 (28.0–78.0)	67.0±8.1 (40.0–78.0)	67.3±8.2 (28.0–78.0)
ADCS-iADL score††	48.9±7.6 (21.0–59.0)	48.4±7.5 (24.0–59.0)	48.8±7.5 (21.0–59.0)
MMSE score‡‡	23.6±3.1 (14.0–29.0)	23.7±2.9 (16.0–29.0)	23.5±3.1 (13.0–30.0)
Amyloid plaque level on florbetapir PET — centiloids (range)	107.6±36.0 (41.0–251.4)	101.1±33.3 (38.7–225.2)	104.2±34.8 (38.7–251.4)
Global tau load on flortaucipir PET — mean (range)§§	0.47±0.19 (0.1–1.2)	0.46±0.15 (0.2–0.9)	0.46±0.17 (0.1–1.2)

* Plus–minus values are means ±SD. PET denotes positron-emission tomography. Percentages may not total 100 because of rounding.
† The total includes participants assigned to the combination-therapy group, which was discontinued.
‡ Race and ethnic group were reported by the participant. Categories of other race included multiple and American Indian or Alaska Native.
§ On the Integrated Alzheimer's Disease Rating Scale (iADRS), scores range from 0 to 144, with lower scores indicating a greater cognitive deficit and greater impairment of the ability to perform activities of daily living. Data were available for 130 participants in the donanemab group and 271 total.
¶ On the Clinical Dementia Rating Scale–Sum of Boxes (CDR-SB), scores range from 0 to 18, with higher scores indicating greater impairment.
‖ On the 13-item cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-Cog$_{13}$), scores range from 0 to 85, with higher scores indicating a greater deficit.
** On the Alzheimer's Disease Cooperative Study–Activities of Daily Living Inventory (ADCS-ADL), scores range from 0 to 78, with lower scores indicating greater impairment. Data were available for 130 participants in the donanemab group and 271 total.
†† On the Alzheimer's Disease Cooperative Study–Instrumental Activities of Daily Living Inventory (ADCS-iADL), scores range from 0 to 59, with lower scores indicating greater impairment. Data were available for 130 participants in the donanemab group and 271 total.
‡‡ On the Mini–Mental State Examination (MMSE), scores range from 0 to 30, with higher scores indicating better mental performance. Data were available for 126 participants in the donanemab group, 121 in the placebo group, and 261 total.
§§ Data were available for 130 participants in the donanemab group, 124 in the placebo group, and 269 total.

A Primary Outcome: iADRS Score



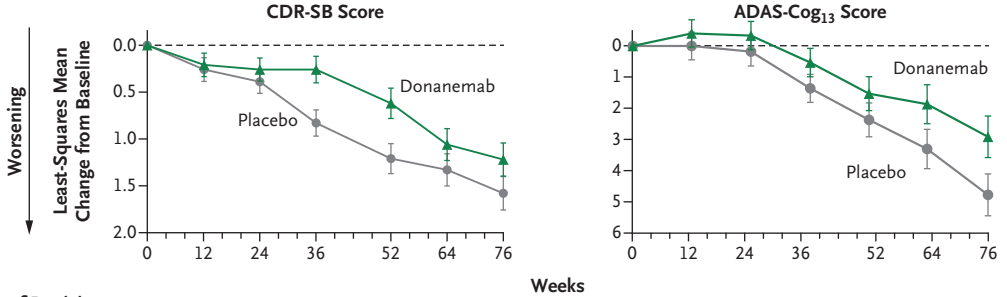
Difference in Least-Squares Mean Change

	Donanemab vs. placebo (points)	95% CI
Wk 36	2.44±0.96	0.55–4.33
Wk 52	3.67±1.26	1.19–6.15
Wk 64	3.42±1.42	0.63–6.21
Wk 76	3.20±1.56	0.12–6.27

No. of Participants

Donanemab	125	120	112	102	88	89	93
Placebo	120	113	110	103	90	90	91

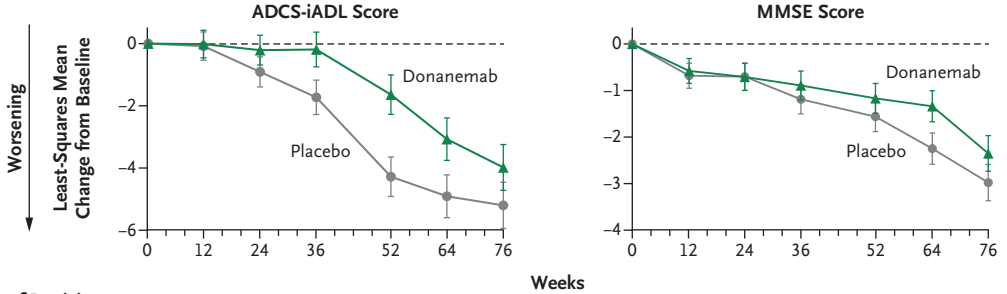
B Secondary Outcomes



No. of Participants

Donanemab	125	122	114	102	90	92	93
Placebo	120	115	111	104	91	90	90

Donanemab	125	121	112	103	89	91	93
Placebo	120	116	111	104	92	90	93



No. of Participants

Donanemab	125	121	114	102	89	90	93
Placebo	120	114	110	104	90	90	91

Donanemab	121	118	108	100	86	89	91
Placebo	115	112	107	101	89	87	90

C Primary and Secondary Outcomes, MMRM and Bayesian Analysis

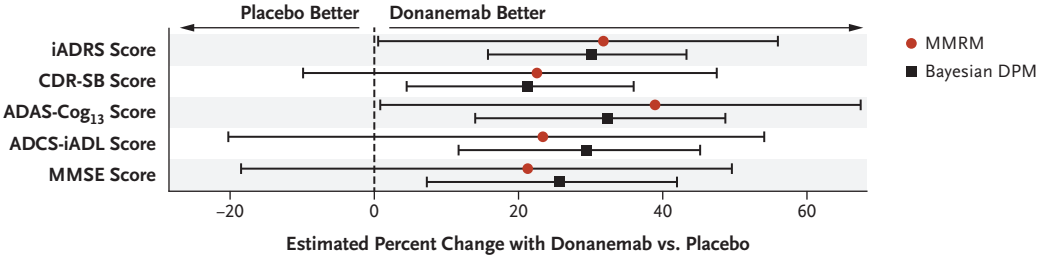


Figure 2 (facing page). Primary and Secondary Clinical Outcomes.

Panel A shows the results for the primary outcome, the least-squares mean change from baseline to 76 weeks in the score on the Integrated Alzheimer's Disease Rating Scale (iADRS; scores range from 0 to 144, with lower scores indicating a greater cognitive deficit and greater impairment of the ability to perform activities of daily living), in the donanemab group and the placebo group, analyzed with a mixed model for repeated measures (MMRM). The difference between the donanemab group and the placebo group in the primary outcome was 3.20 (95% confidence interval [CI], 0.12 to 6.27; P=0.04). Panel B shows the results for secondary clinical outcomes, including the least-squares mean change from baseline to 76 weeks in scores on the Clinical Dementia Rating Scale–Sum of Boxes (CDR-SB; scores range from 0 to 18, with higher scores indicating greater impairment), the 13-item cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-Cog_{13}; scores range from 0 to 85, with higher scores indicating a greater deficit), the Alzheimer's Disease Cooperative Study–Instrumental Activities of Daily Living Inventory (ADCS-iADL; scores range from 0 to 59, with lower scores indicating greater impairment), and the Mini–Mental State Examination (MMSE; scores range from 0 to 30, with higher scores indicating better mental performance), in the donanemab group and the placebo group, analyzed with the MMRM. Panel C shows the estimated percent change in the iADRS, CDR-SB, ADAS-Cog_{13}, ADCS-iADL, and MMSE scores in the donanemab group as compared with the placebo group, analyzed with the MMRM at 76 weeks (with 95% confidence intervals) and with the Bayesian disease progression model (DPM) over the entire 18-month intervention period (with 95% credible intervals). The credible intervals for data in the Bayesian disease progression model were not adjusted for multiple comparisons, and no definite conclusions can be drawn. Plus–minus values are means ±SE. I bars indicate standard errors.

amyloid plaque level of <24.10 centiloids) at 24, 52, and 76 weeks was 40.0%, 59.8%, and 67.8%, respectively (Fig. 3A). In addition, approximately 27.4% and 54.7% of participants in the donanemab group had sufficient lowering of the amyloid plaque level to switch to placebo infusion at 28 and 56 weeks, respectively. Evaluation of the change from baseline to 76 weeks in the global tau load as assessed by flortaucipir PET did not show a substantial difference between groups (Fig. 3B), nor did evaluation of the change in hippocampal volume as assessed by volumetric MRI (Fig. 3C). At 52 and 76 weeks, volumetric MRI showed a greater decrease in whole-brain volume and a greater increase in ventricular volume in the donanemab group than in the placebo group (Fig. 3C).

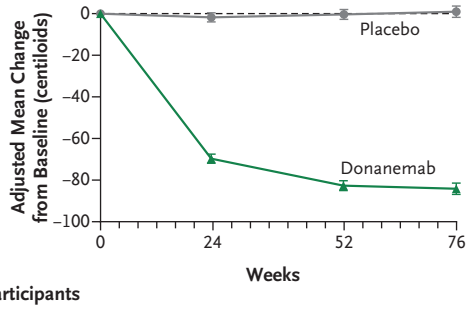
ADVERSE EVENTS

There was no significant difference between the donanemab group and the placebo group in the incidence of death or serious adverse events (Table 2). In the safety population, 119 of 131 participants (90.8%) in the donanemab group and 113 of 125 participants (90.4%) in the placebo group had at least one adverse event during the double-blind intervention period. The incidence of ARIA-E was significantly higher in the donanemab group than in the placebo group (26.7% vs. 0.8%) (Table 2). Symptomatic ARIA-E was reported by 6.1% of all participants in the donanemab group (22% of those with ARIA-E), as compared with 0.8% of all participants in the placebo group. Most cases of ARIA-E occurred at or by week 12 of the intervention period. Serious symptomatic ARIA-E that led to hospitalization occurred in 2 participants (1.5%) in the donanemab group; both participants had symptoms of confusion and 1 reported difficulty with expressing herself. ARIA-E and the associated symptoms resolved in both participants, with a mean ARIA-E resolution time of 18 weeks. Figure S1 shows results for the primary outcome among participants with and without ARIA-E. In the donanemab group, 7 participants (5.3%) discontinued treatment and 2 (1.5%) discontinued the trial because of ARIA-E. No brain macrohemorrhages were seen in either trial group. The incidences of superficial siderosis of the central nervous system (a type of ARIA with hemosiderin deposits [ARIA-H]), nausea, and infusion-related reactions were greater in the donanemab group than in the placebo group (Table 2). Infusion-related reactions were reported by 7.6% of participants in the donanemab group and none in the placebo group. Serious infusion-related reactions or hypersensitivity occurred in 3 participants (2.3%) in the donanemab group. A summary of all serious adverse events is provided in Table S4. Antidrug antibodies were detected during the intervention period in approximately 90% of the participants who were treated with donanemab.

DISCUSSION

In this trial of donanemab, an amyloid plaque–specific intervention, in participants with early symptomatic Alzheimer's disease, the primary analysis showed a smaller reduction in the iADRS

A Amyloid Plaque Level on Florbetapir PET

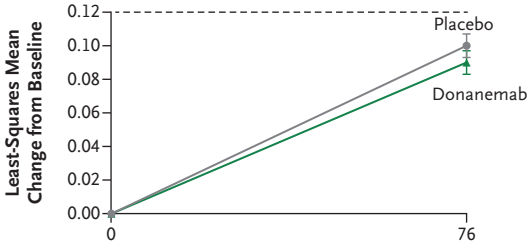


	Difference in Adjusted Mean Change		Amyloid-Negative Status, Donanemab
	Donanemab vs. placebo	95% CI	
	centiloids		*no. (%)*
Wk 24	−67.83±3.16	−74.04 to −61.61	46 (40.0)
Wk 52	−82.30±3.41	−89.02 to −75.59	55 (59.8)
Wk 76	−85.06±3.87	−92.68 to −77.43	61 (67.8)

No. of Participants

Donanemab	121	115	92	90
Placebo	112	111	91	91

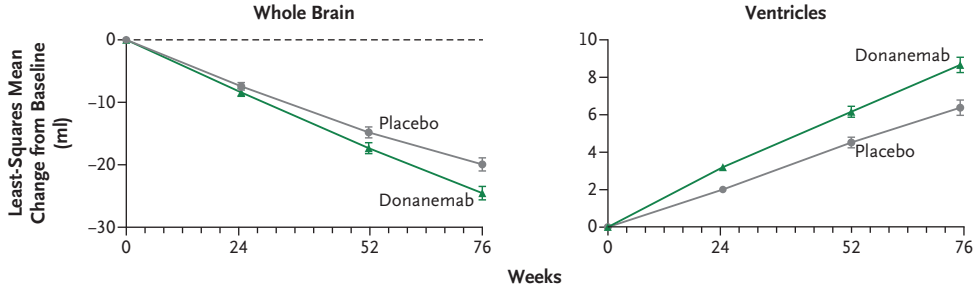
B Global Tau Load on Flortaucipir PET



No. of Participants

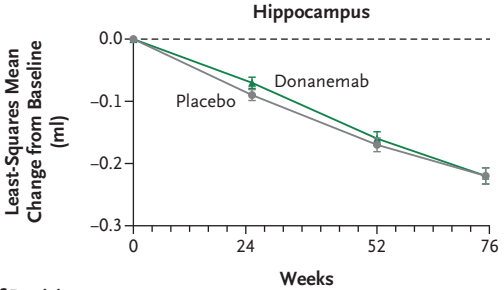
Donanemab	90			90
Placebo	87			87

C Results on Volumetric MRI



No. of Participants

Donanemab	124	103	86	82	124	103	86	82
Placebo	119	108	89	83	119	108	89	83



No. of Participants

Donanemab	124	103	86	82
Placebo	119	108	89	83

Figure 3 (facing page). Secondary Biomarker Outcomes.
Results are shown for secondary biomarker outcomes, including the change from baseline to 76 weeks in the level of amyloid plaques deposited in the brain as assessed by positron-emission tomography (PET) with injection of ^{18}F-florbetapir (Panel A), in the global tau load as assessed by PET with injection of ^{18}F-flortaucipir (Panel B), and in the whole-brain volume, ventricular volume, and hippocampal volume as assessed by volumetric magnetic resonance imaging (MRI) (Panel C). Amyloid-negative status is defined as an amyloid plaque level of less than 24.10 centiloids, which is the average level among otherwise healthy persons of a similar age. Plus–minus values are means ±SE. I bars indicate standard errors.

score, by 3.20 points, in the donanemab group than in the placebo group. The iADRS ranges from 0 to 144. The minimal clinically important difference on this scale has not been established, but because we aimed to find a medicine that could slow Alzheimer's disease progression by at least half, the trial was powered to show a 6-point difference (decreases from baseline of approximately 12 and 6 points for placebo and donanemab, respectively); this goal was not reached. For most secondary outcomes, differences between the two groups did not provide clinical support for efficacy of donanemab in the MMRM analyses but showed support in a Bayesian disease progression model, in which credible intervals were not adjusted for multiple comparisons. There was a greater reduction in the amyloid plaque level in the donanemab group than in the placebo group, for which we were unable to show an association with clinical outcomes at the individual level.

Several features of the trial design should be considered. First, the donanemab dosing regimen was selected to facilitate aggressive removal of amyloid plaques early in the trial, and almost 60% of participants had amyloid-negative status by 52 weeks. Second, all the participants were required to meet flortaucipir PET screening criteria, which may have narrowed the range of underlying pathologic features and in turn decreased variation in clinical decline. Third, the flortaucipir PET screening criteria led to the exclusion of patients with the highest tau levels, who are hypothesized to have disease that is more resistant to antiamyloid treatments. Finally, as proposed by the European Prevention of Alzheimer's Dementia project, analyses of treatment effects on the iADRS, ADAS-Cog$_{13}$, ADCS-iADL, CDR-SB, and MMSE scores were performed with the use of the Bayesian disease progression model.[35] Given its better sensitivity for detecting treatment effects, this model can allow for gains in statistical power[34]; in this trial, the model produced estimates of disease slowing that were similar to the single point estimate of the MMRM.

With regard to the observed lack of treatment effect on the global tau load, it is possible that global tau changes on PET lag as compared with amyloid changes on PET and that an 18-month period is too short to detect global tau changes. Models involving patients with autosomal dominant Alzheimer's disease have suggested a lag of 10 to 20 years from the first detection of PET amyloid changes to the first detection of PET tau changes.[36] The lack of effect on the global tau load prompts questions about whether targeting Aβ reduction affects biologic disease progression. However, in this trial, additional prespecified analyses of brain regions suggested a greater reduction in tau accumulation in frontal and temporal lobe regions in the donanemab group than in the placebo group (Fig. S2).

No significant change in hippocampal volume was observed in this trial, whereas recent trials of BACE1 inhibitors showed significant volume changes.[31] The implications of this finding of retained hippocampal volume are unclear. The observations of a greater decrease in whole-brain volume and a greater increase in ventricular volume with donanemab than with placebo are paradoxical and need further investigation. Global changes on volumetric MRI have typically been attributed to atrophy in studies of the natural history of Alzheimer's disease, but it remains unclear whether they represent atrophy in the context of rapid structural removal of protein aggregates, as was seen in this trial and in another study of antiamyloid therapy.[37]

ARIA-E occurred in approximately one in four participants in the donanemab group, with 6.1% reporting symptomatic ARIA-E. There was a higher incidence of ARIA-E among *APOE* ε4 carriers, a finding similar to observations in other trials of plaque-targeting antibodies.[38-41] The incidence of antidrug antibodies in participants

Table 2. Summary of Adverse Events.*

Event	Donanemab (N=131)	Placebo (N=125)	P Value
Death — no (%)	1 (0.8)	2 (1.6)	0.62
Serious adverse event — no. (%)†	23 (17.6)	22 (17.6)	>0.99
Adverse event that led to discontinuation of intervention — no. (%)‡	40 (30.5)	9 (7.2)	<0.001
Adverse event that led to discontinuation of trial — no. (%)‡	20 (15.3)	6 (4.8)	0.007
Adverse event that occurred during the intervention period — no. (%)	119 (90.8)	113 (90.4)	>0.99
Adverse event that occurred during the intervention period in ≥5% of participants in either group — no. (%)			
ARIA-E	35 (26.7)	1 (0.8)	<0.001
Fall	17 (13.0)	19 (15.2)	0.72
Dizziness	11 (8.4)	15 (12.0)	0.41
Headache	10 (7.6)	15 (12.0)	0.29
Superficial siderosis of central nervous system	18 (13.7)	4 (3.2)	0.003
Arthralgia	10 (7.6)	10 (8.0)	>0.99
Nausea	14 (10.7)	4 (3.2)	0.03
Upper respiratory tract infection	9 (6.9)	9 (7.2)	>0.99
Urinary tract infection	13 (9.9)	5 (4.0)	0.09
Diarrhea	11 (8.4)	5 (4.0)	0.20
ARIA-H	11 (8.4)	4 (3.2)	0.11
Cerebral microhemorrhage	10 (7.6)	3 (2.4)	0.09
Infusion-related reaction	10 (7.6)	0	0.002
Pneumonia	7 (5.3)	5 (4.0)	0.77
Depression	6 (4.6)	8 (6.4)	0.59
Contusion	0	10 (8.0)	<0.001
Vomiting	7 (5.3)	3 (2.4)	0.34
Anxiety	7 (5.3)	2 (1.6)	0.17
ARIA Event§	**Donanemab (N=131)**	**Placebo (N=125)**	**Total (N=256)**
ARIA-E or ARIA-H — no. (%)	51 (38.9)	10 (8.0)	61 (23.8)
ARIA-E			
Any — no. (%)	36 (27.5)	1 (0.8)	37 (14.5)
Symptom status — no. (%)			
Asymptomatic	28 (21.4)	0	28 (10.9)
Symptomatic	8 (6.1)	1 (0.8)	9 (3.5)
APOE genotype — no./total no. (%)			
ε2/ε3	0/1	0/1	0/2
ε2/ε4	0/2	0/2	0/4
ε3/ε3	4/35 (11.4)	0/31	4/66 (6.1)
ε3/ε4	21/68 (30.9)	0/62	21/130 (16.2)
ε4/ε4	11/25 (44.0)	1/28 (3.6)	12/53 (22.6)

Table 2. (Continued.)

Event	Donanemab (N=131)	Placebo (N=125)	P Value
ARIA-H — no. (%)			
Any	40 (30.5)	9 (7.2)	49 (19.1)
Microhemorrhage	26 (19.8)	6 (4.8)	32 (12.5)
Superficial siderosis	23 (17.6)	3 (2.4)	26 (10.2)
Macrohemorrhage	0	0	0

* ARIA denotes amyloid-related imaging abnormalities, ARIA-E ARIA with edema or effusions, and ARIA-H ARIA with hemosiderin deposits.
† A summary of all serious adverse events is provided in Table S4.
‡ Discontinuation was based on protocol-defined criteria or reasons cited by the participant or the principal investigator.
§ ARIA events were based on central review of magnetic resonance imaging studies and include events that occurred beyond the double-blind intervention period.

who were treated with donanemab was approximately 90%.

Limitations of the trial include enrollment of 257 participants and few non-White participants. Changes in donanemab dosing due to ARIA-E and the criteria regarding amyloid plaque reduction on florbetapir PET resulted in heterogeneity of the doses received. The occurrence of ARIA-E may have led to unblinding; however, the iADRS scores were similar, by visual inspection of the curves, in participants with ARIA-E and those without ARIA-E. Finally, the incidence of trial discontinuation due to adverse events was higher among participants who were treated with donanemab, introducing survivor bias. Because of the Covid-19 pandemic, investigative sites were allowed to replace on-site visits with telephone visits for any visit except the final visit at 76 weeks; efficacy data were not collected and the trial drug was not dispensed at telephone visits. Because missed assessments were not allowed to occur at the final visit, the effect on interpretation of the analyses was considered to be minimal.

This randomized phase 2 trial showed that, in patients with early symptomatic Alzheimer's disease, treatment with donanemab resulted in modestly less cognitive and functional decline than placebo; however, slowing disease progression by half (an assumption on which the power calculation was based) was not achieved, and treatment resulted in amyloid-related imaging abnormalities. Longer and larger trials are required to study the efficacy and safety of donanemab in early Alzheimer's disease. TRAILBLAZER-EXT (ClinicalTrials.gov number, NCT04640077), a follow-on study for those who participated in TRAILBLAZER-ALZ, is currently enrolling participants.

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Dr. Mintun reports being employed by and owning shares in Eli Lilly and being employed by Avid Radiopharmaceuticals; Dr. Lo, being employed by and owning stocks and shares in Eli Lilly; Dr. Duggan Evans, being employed by and owning stocks in Eli Lilly; Dr. Wessels, being employed by and owning shares in Eli Lilly; Dr. Ardayfio, being employed by and owning stocks in Eli Lilly; Dr. Andersen, being employed by and owning shares in Eli Lilly; Dr. Shcherbinin, being employed by and owning stocks in Eli Lilly; Dr. Sparks, being employed by and owning stocks in Eli Lilly; Dr. Sims, being employed by and owning stocks in Eli Lilly; Dr. Brys, being employed by and owning stocks in Eli Lilly; Dr. Apostolova, receiving donated supplies from Avid Radiopharmaceuticals, grant support and research support from Roche Diagnostics, research support from Life Molecular Imaging, and consulting fees from Biogen and Two Labs and serving on a data and safety monitoring board for IQVIA; Dr. Salloway, receiving grant support and consulting fees from Biogen, Eisai, Eli Lilly, Genentech, and Roche and consulting fees and travel support from Avid Radiopharmaceuticals; and Dr. Skovronsky, being employed by and owning shares in Eli Lilly. No other potential conflict of interest relevant to this article was reported.

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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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