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Association of Amyloid Reduction After Donanemab Treatment With Tau Pathology and Clinical Outcomes
The TRAILBLAZER-ALZ Randomized Clinical Trial

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IMPORTANCE β-amyloid plaques and neurofibrillary tau deposits biologically define Alzheimer disease.

OBJECTIVE To perform post hoc analyses of amyloid reduction after donanemab treatment and assess its association with tau pathology and clinical measures.

DESIGN, SETTING, AND PARTICIPANTS The Study of LY3002813 in Participants With Early Symptomatic Alzheimer's Disease (TRAILBLAZER-ALZ) was a phase 2, placebo-controlled, randomized clinical trial conducted from December 18, 2017, to December 4, 2020, with a double-blind period of up to 76 weeks and a 48-week follow-up period. The study was conducted at 56 centers in the US and Canada. Enrolled were participants from 60 to 85 years of age with gradual and progressive change in memory function for 6 months or more, early symptomatic Alzheimer disease, elevated amyloid, and intermediate tau levels.

INTERVENTIONS Donanemab (an antibody specific for the N-terminal pyroglutamate β-amyloid epitope) dosing was every 4 weeks: 700 mg for the first 3 doses, then 1400 mg for up to 72 weeks. Blinded dose-reduction evaluations occurred at 24 and 52 weeks based on amyloid clearance.

MAIN OUTCOMES AND MEASURES Change in amyloid, tau, and clinical decline after donanemab treatment.

RESULTS The primary study randomized 272 participants (mean [SD] age, 75.2 [5.5] years; 145 female participants [53.3%]). The trial excluded 1683 of 1955 individuals screened. The rate of donanemab-induced amyloid reduction at 24 weeks was moderately correlated with the amount of baseline amyloid (Spearman correlation coefficient *r*, −0.54; 95% CI, −0.66 to −0.39; *P* < .001). Modeling provides a hypothesis that amyloid would not reaccumulate to the 24.1-centiloid threshold for 3.9 years (95% prediction interval, 1.9-8.3 years) after discontinuing donanemab treatment. Donanemab slowed tau accumulation in a region-dependent manner as measured using neocortical and regional standardized uptake value ratios with cerebellar gray reference region. A disease-progression model found a significant association between percentage amyloid reduction and change on the integrated Alzheimer Disease Rating Scale only in apolipoprotein E (*APOE*) ε4 carriers (95% CI, 24%-59%; *P* < .001).

CONCLUSIONS AND RELEVANCE Results of post hoc analyses for donanemab-treated participants suggest that baseline amyloid levels were directly associated with the magnitude of amyloid reduction and inversely associated with the probability of achieving complete amyloid clearance. The donanemab-induced slowing of tau was more pronounced in those with complete amyloid clearance and in brain regions identified later in the pathologic sequence. Data from other trials will be important to confirm aforementioned observations, particularly treatment response by *APOE* ε4 status.

TRIAL REGISTRATION ClinicalTrials.gov Identifier: NCT03367403

Visual Abstract

Supplemental content

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Donanemab is an immunoglobulin G1 antibody specific for an epitope that is only present in mature brain amyloid plaques.[1,2] Donanemab treatment resulted in rapid and deep clearance of amyloid plaques as shown by [^{18}F] florbetapir positron emission tomography (PET) in phase 1 studies.[1,3]

The Study of LY3002813 in Participants With Early Symptomatic Alzheimer's Disease (TRAILBLAZER-ALZ) trial[2] was a multicenter, double-blind, phase 2, placebo-controlled, randomized clinical trial that assessed the safety and efficacy of donanemab in participants with early symptomatic Alzheimer disease (AD) who had intermediate tau and elevated amyloid deposition on PET.[2] It was designed to facilitate rapid removal of amyloid plaques early in the trial and, therefore, to maximize the time at lowered plaque load and enhance the opportunity to detect clinical benefit. After 24 (or 52) weeks of treatment, some participants were switched to a lower dose or placebo based on florbetapir scan results.

The TRAILBLAZER-ALZ study met its primary objective, with donanemab slowing the clinical decline of AD relative to placebo by 32% as assessed via mixed model for repeated measures analysis of the integrated AD Rating Scale (iADRS) score at 76 weeks. This slowing of clinical decline was associated with a substantial amyloid plaque lowering, with a difference in an adjusted mean change between donanemab and placebo of 85 centiloids (CL) at 76 weeks. In addition, 68% of donanemab-treated participants achieved amyloid-negative status, defined as an amyloid plaque level of less than 24.1 CL (complete amyloid clearance)[4] by 76 weeks.

No substantial treatment effect on the global tau load[5] occurred as determined using a Tau^{IQ} algorithm (Invicro)[5]; however, our exploratory analyses showed significantly greater slowing of tau pathology in key brain regions for donanemab vs placebo.[2]

In these exploratory post hoc analyses, we further investigated donanemab-induced amyloid reduction and examined associations between amyloid lowering and tau PET. In particular, the association between achieving early plaque clearance after 24 weeks and downstream effects on tau pathology progression in multiple brain regions over a longer, 76-week period of time was explored. To reveal the underlying trends, we developed 3 models to explore the sustainability of amyloid reduction (exposure-response model), the association between plaque lowering and tau pathology (mediation model), and the association between plaque lowering and clinical benefits (disease-progression model).

Key Points

Question Is donanemab-induced amyloid reduction associated with slowing of tau pathology and clinical decline in individuals with Alzheimer disease?

Findings In early symptomatic Alzheimer disease, donanemab induced a robust decrease in amyloid plaque levels by 24 weeks, with baseline plaque directly associated with magnitude of amyloid reduction and inversely associated with probability of complete clearance. In individuals with amyloid clearance, post hoc modeling suggests that amyloid levels would remain below the positivity threshold for almost 4 years without treatment; in treated patients, greater plaque clearance was associated with slower progression of tau positron emission tomography and slower clinical decline (in apolipoprotein E ε4 carriers only).

Meaning Exploratory post hoc analyses of the Study of LY3002813 in Participants With Early Symptomatic Alzheimer's Disease (TRAILBLAZER-ALZ) identified potential associations between amyloid lowering, tau pathology, and clinical outcomes.

Methods

Participants and Study Design

The TRAILBLAZER-ALZ eligibility criteria and study design were previously published (Supplement 1; eMethods in Supplement 2).[2] The study was reviewed and approved by appropriate local ethics committees, and written informed consent was obtained from study participants. Race and ethnicity were not reported in this article as neither was a subgroup for any analyses in this investigation. The primary study enrolled participants with AD who had an intermediate tau level (moderate AD patterns based on visual assessment and standardized uptake value ratio [SUVR] between 1.10 and 1.46, inclusive, or advanced AD patterns and SUVR ≤1.46[2,6]) plus elevated amyloid level (equivalent to ≥37 CL). To determine an intermediate tau level, a previously published AD signature-weighted neocortical SUVR[7] with respect to a reference signal intensity in white matter (PERSI[8]) was used.

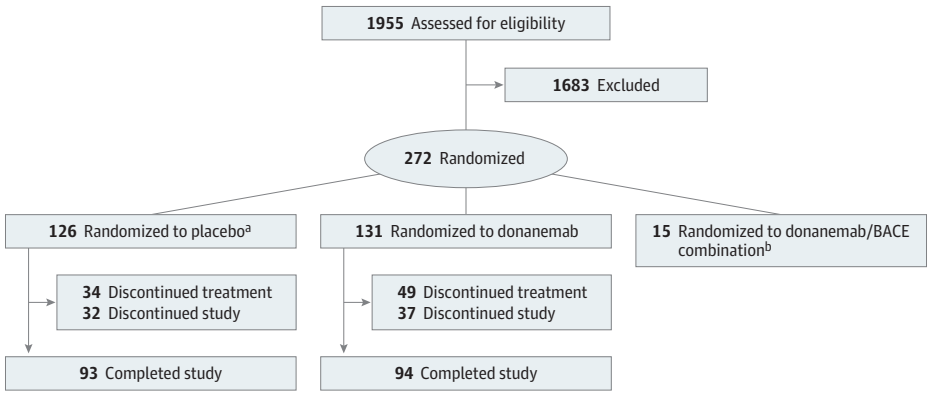
A dose change (blinded to participants, sites, and sponsor) was possible depending on the amyloid level measured using florbetapir scans at weeks 24 and 52. Specifically, participants in the donanemab group were titrated down from 1400 mg to 700 mg if amyloid PET levels decreased to the range of 11 CL to less than 25 CL, or to placebo if less than 11 CL at any single scan, or 11 CL to less than 25 CL for 2 consecutive amyloid measures.

Of note, depending on the data availability and analysis nature, not all participants mentioned in **Figure 1** were included in the post hoc examinations reported in this study. Participant numbers are referenced for each analysis. This study followed the Consolidated Standards of Reporting Trials (CONSORT) reporting guidelines.

Florbetapir PET

Detailed PET acquisition and processing methods can be found in the eMethods in Supplement 2. Participants were considered to achieve complete amyloid plaque clearance if posttreatment amyloid level was below an amyloid threshold of 24.1 CL, which is the same threshold required for amyloid levels consistent with a diagnosis of AD.[2,4] Importantly, the thresholds of 11 and 24.1 CL are very close to ones found in the PET-autopsy study to detect moderate to frequent plaques and intermediate to high AD neuropathological changes, respectively.[9] Donanemab-treated participants who did not meet the complete clearance definition at the first 24-week PET scan were considered to have early partial clearance.

Figure 1. Patient Flowchart



BACE indicates β-site amyloid precursor protein cleaving enzyme.

[a] One participant was randomly assigned to placebo but discontinued before receiving an infusion.

[b] Combination therapy was discontinued from the study in the protocol amendment (Supplement 1).

Flortaucipir PET

Detailed PET acquisition and processing methods can be found in the eMethods in Supplement 2. A previously published cerebellar gray matter region derived from the cerebellar crustaneous atlas-based region[10] was used as a reference in these post hoc exploratory longitudinal tau SUVR calculations. Global cortical tau level was measured using a previously published AD signature-weighted neocortical SUVR.[7]

For regional tau SUVR calculations, regions of interest from the Automated Anatomical Labeling (AAL)[7,10] atlas belonging to temporal, parietal, and frontal cortical areas were used. Those 3 lobes were selected based on the lobar classification approach[11] constituting an anatomical dependence of tau accumulation. In addition, we examined the change in tau SUVR on 17 predetermined AAL regions belonging to the temporal, parietal, and frontal lobes. We used an independent tau PET data set to order those regions into a pathologic spreading sequence using an event-based modeling[12,13] (eMethods in Supplement 2). To explore the connection between amyloid reduction and downstream tau progression, we analyzed the change in tau over 76 weeks for the following 3 groups: placebo-treated participants, participants treated with donanemab who reached a complete amyloid clearance in the first 24 weeks, and participants treated with donanemab who did not attain a complete amyloid clearance in the first 24 weeks (partial clearance).

Exposure-Response Model

Change in amyloid owing to treatment with donanemab was analyzed using an indirect response model, by way of nonlinear mixed-effect modeling. The model incorporated all available longitudinal pharmacokinetic (PK) and PET data (baseline, weeks 24, 52, and 76; 304 participants from both the phase 1b donanemab study and TRAILBLAZER-ALZ[1,2,14]). Treatment and placebo groups as well as dosing information for each participant were included in the modeling. The effect of PK was assessed, using nonlinear mixed-effect regression with a treatment effect simulating the amyloid plaque degradation rate constant; individual participant baseline amyloid plaque level was an initial condition at time 0. The model was parameterized in terms of the half-life of plaque degradation, the initial amyloid plaque level, the extent to which donanemab enhanced plaque removal, and the donanemab concentration associated with enhanced plaque removal. The modeling process is described in greater detail in eMethods in Supplement 2.

Clinical Outcome

The primary outcome in TRAILBLAZER-ALZ was the change from baseline in the score on the iADRS[15] (range, 0-144, with lower scores indicating greater cognitive and functional impairment[2]) at 76 weeks. The iADRS is a linear combination of the 13-item cognitive subscale of the AD Assessment Scale[16] and the AD Cooperative Study-Instrumental Activities of Daily Living Inventory.[17] The iADRS has been validated, and statistical properties of the composite performance have been described[18,19]; it has been used as a clinical outcome measure in previous phase 3 trials in AD.[20,21]

Disease Progression Model

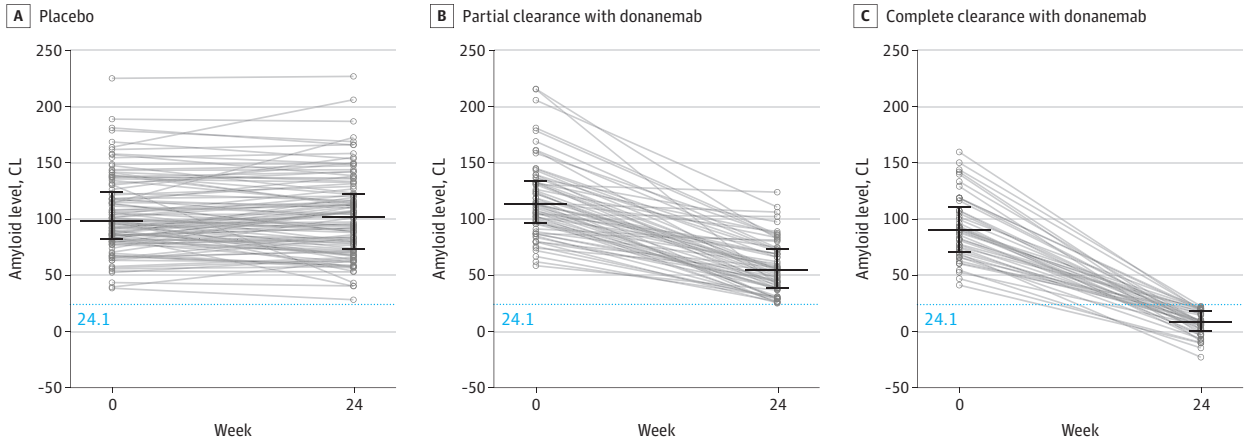
Analysis assessing the association between amyloid reduction and the slowing of cognitive decline was conducted using a disease-progression model comprising a Richard logistic model with beta regression to account for decreasing variance in residual error as data approached the boundaries of the cognitive scales, similar to previously published models.[22] The model was developed using all available PK, amyloid PET, and iADRS data. In this model, change in iADRS was used to estimate disease progression. Each individual's percentage change from baseline plaque level, as estimated using the amyloid reduction model, was used as a time-varying covariate in the model to estimate the change in rate of disease progression in the overall population (donanemab and placebo). Apolipoprotein E (*APOE*) ε4 carrier status was investigated as a potential covariate on the association between amyloid removal and change in disease progression. Additional detail is provided in the eMethods in Supplement 2.

Statistical Analyses

Correlations

The associations between baseline and change values from various amyloid and tau PET measurements were examined using Spearman rank correlation analyses. Analysis of cova-

Figure 2. Association Between Amyloid Levels and the Magnitude of Amyloid Change at 24 Weeks



Median (IQR) amyloid levels (in centiloid [CL] units) at baseline and 24 weeks for participants receiving placebo (A), donanemab-treated participants with partial amyloid clearance at week 24 (B), and donanemab-treated participants with complete amyloid clearance at week 24 (C) demonstrating the change owing to donanemab treatment. Mean (SD) values along with partial vs complete amyloid clearance and treatment vs placebo comparisons can be found in eTable 2 in Supplement 2. Only participants with follow-up positron emission tomography scans are included.

riance (ANCOVA) was used to compare the differences of tau change values by treatment groups (placebo, complete amyloid clearance at 24 weeks, and partial amyloid clearance at 24 weeks). The ANCOVA models were adjusted for baseline measure and age. When comparing the participant's baseline characteristics, 2-sample *t* test was used for continuous variables, and Fisher exact test was used for categorical variables.

Probability of Complete Clearance

To evaluate the effect of baseline amyloid levels on the probability of participants to reach complete amyloid clearance at 24, 52, and 76 weeks, 3 logistic regressions were run respectively, with amyloid PET results (complete clearance or partial clearance) at weeks 24, 52, and 76 as the dependent variables, and baseline amyloid PET as the only independent variable. Probabilities of reaching complete clearance were provided along with corresponding 95% CIs.

Mediation Model

A mediation model was used to test the association of amyloid change in relation to global cortical tau level as measured using an AD signature–weighted neocortical SUVR (eMethods in Supplement 2).[7] Data were analyzed using the lavaan package (0.6-5)[23] in R Studio, version 1.4.1717-3. All *P* values were 2-sided, and a *P* value < .05 was considered statistically significant.

Results

Participants

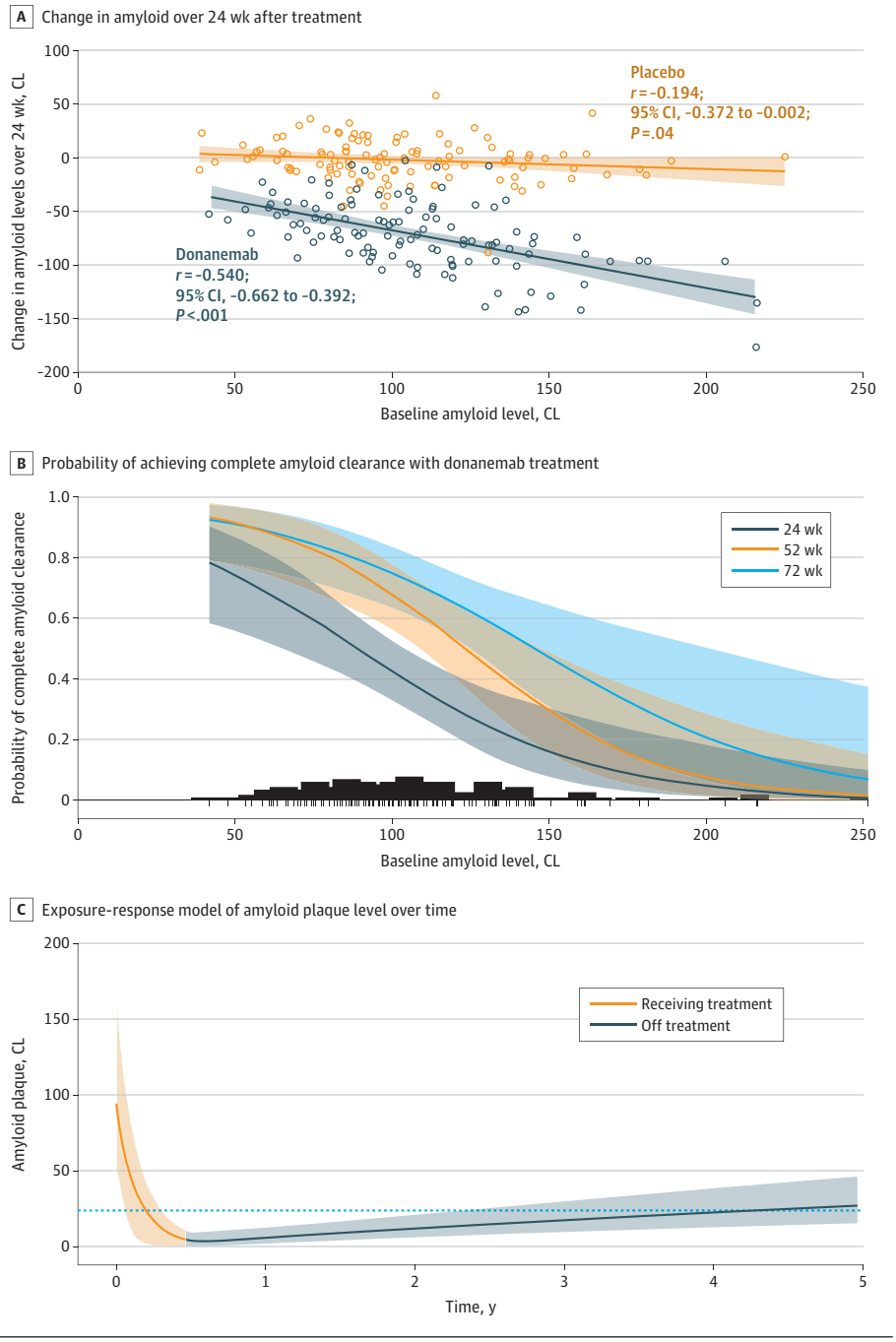
Enrollment, randomization, and completion of the TRAILBLAZER-ALZ study is illustrated in Figure 1, and demographics of the population were previously described.[2] Briefly, the primary study randomized 272 participants (mean [SD] age, 75.2 [5.5] years; 127 male participants [46.7%]; 145 female participants [53.3%]). The trial excluded 1683 of 1955 individuals screened. The demographic and baseline characteristic data based on 24-week amyloid status of those with follow-up PET scans explored in these post hoc analyses can be found in the supplement (eTable 1 in Supplement 2).

Donanemab-Induced Amyloid Reduction

Individual amyloid trajectories show that in contrast to placebo, donanemab induced a robust amyloid plaque reduction in essentially all participants at 24 weeks (**Figure 2**). Although the donanemab group average at baseline exceeded 107 CL, it approached the florbetapir PET eligibility threshold in the first 24 weeks with a mean (SD) value of 37.1 (30.9) CL (eTable 2 in Supplement 2). Importantly, 40% of donanemab-treated participants (46 of 115) reached a complete amyloid clearance threshold of 24.1 CL (derived from eTable 1 in Supplement 2). It is important to note that the average baseline amyloid levels of participants with complete amyloid clearance at 24 weeks (mean [SD], 92.8 [28.7] CL) was significantly lower compared with those who had partial amyloid clearance (mean [SD], 117.4 [33.9] CL) (eTable 1 in Supplement 2). At 24 weeks, the mean (SD) amyloid for the complete clearance group was 7.7 (10.8) CL and that of the partial clearance group was 56.7 (23.5) CL (eTable 2 in Supplement 2). The average amyloid level for placebo-treated participants did not change appreciably, and none attained complete amyloid clearance at 24 weeks (Figure 2A).

When analyzing factors influencing the variability of donanemab-induced amyloid lowering, we found a moderate correlation (Spearman correlation coefficient *r*, −0.54; 95% CI, −0.66 to −0.39; *P* < .001) between the plaque level at baseline and the total amount of plaque removed in the first 24 weeks after donanemab treatment (**Figure 3**A). Specifically, individuals with a greater baseline amyloid plaque level had, on average, greater amyloid plaque removal. However, despite experiencing greater plaque reduction, participants with greater

Figure 3. Amyloid Responses to Initiation and Discontinuation of Treatment



A, The change in amyloid over 24 weeks after treatment is dependent on baseline amyloid levels. B, Three logistic regression curves to estimate the probability of achieving complete amyloid clearance with donanemab after 24, 52, and 72 weeks of donanemab treatment. The black bars represent the histogram of participants with corresponding baseline amyloid levels. Complete amyloid clearance is defined as having less than 24.1 centiloids (CL). Shaded regions are 95% CIs. C, Exposure-response model of amyloid plaque level over time. Simulated amyloid plaque level over time using treatment exposure-response model (based on 304 participants) and stratified by participants, in the simulation, achieving less than 11 CL by 24 weeks and then discontinuing donanemab treatment. Shaded region indicates 95% prediction interval, the solid line is the predicted median, the orange region depicts participants receiving treatment (to week 24) and then stopping treatment (blue region), and the blue-dotted line displays 24.1 CL plaque clearance threshold.

baseline amyloid levels had a lower probability of reaching the complete amyloid clearance threshold (logistic regression models, Figure 3B). Conversely, less amyloid was removed in participants with lower baseline amyloid plaque levels (Figure 3A), but the probability of achieving complete clearance was greater (logistic regression models, Figure 3B).

Sustainability of Amyloid Reduction

Analysis of the 19 participants who underwent all 4 amyloid PET scans and reached less than 11 CL by 24 weeks (and therefore discontinued donanemab treatment) (eFigure 1 in Supplement 2) showed that the achieved amyloid clearance was sustained with a mean (SD) rate of reaccumulation of 0.02 (7.75) CL per year over the 1-year period in the trial (eFigures 1 and 2 in Supplement 2). In addition, an exposure-response model (model based on data from 304 participants, including data from the phase 1b donanemab study) of amyloid plaque level for all available scans suggests that in participants who achieved an amyloid load of 11 CL or less at week 24 and discontinued amyloid treatment, the median time to reaccumu-

late amyloid from an 11 CL to 24.1 CL threshold could be 3.9 years (95% prediction interval, 1.9-8.3 years) (simulation shown in Figure 3C). These data reinforce the phase 1b results that showed no significant reaccumulation over 72 weeks after a single dose.[1]

Donanemab Slows Tau Accumulation in Cortical Brain Regions

The analysis of weighted neocortical SUVR suggested that donanemab slows tau deposition relative to placebo (**Figure 4**A). A significant 34% slowing of overall tau level, as measured using an adjusted change in that SUVR, was observed for donanemab relative to placebo (derived from eTable 1 in Supplement 2).

Those observations were reinforced using regional analyses. Donanemab slowed tau accumulation over 76 weeks in temporal, parietal, and frontal lobes (Figure 4B-C; eTable 3 in Supplement 2) and in the 17 individual AAL regions (eFigure 3A-B in Supplement 2) with generally less accumulation in participants with complete amyloid plaque clearance at 24 weeks compared with those with partial amyloid clearance. Note that baseline tau level and age are used as covariates in the analyses despite no significant group differences in baseline tau level between participants with complete or partial clearance (eTable 1 in Supplement 2).

Tau accumulation data were ordered according to the pathologic sequence of tau progression. The differences between donanemab and placebo were significant in the regions that accumulate tau later in the cascade, whereas a significant effect was not seen in the temporal inferior region (eFigure 3A in Supplement 2). We also observed that the donanemab-treated participants who achieved complete clearance of amyloid plaque by 24 weeks had nearly complete abrogation of tau progression in a few frontal regions (eFigure 3A in Supplement 2). Similar to the mean change in tau (Figure 4B and eFigure 3A in Supplement 2), donanemab-induced percentage slowing of tau is overall more pronounced in those with complete amyloid clearance and in brain regions identified later in the pathologic sequence (Figure 4C; eFigure 3B in Supplement 2).

We used 3 amyloid reduction parameters to associate with the downstream change in tau over 76 weeks. Those were amyloid level attained at 24 weeks, absolute change in amyloid over 24 weeks, and percentage change in amyloid over 24 weeks (Figure 4D). The Spearman rank correlation analyses confirmed the positive association between amyloid level at 24 weeks and change in regional tau SUVR over 76 weeks among donanemab-treated participants. The association between donanemab-induced percentage change in amyloid over 24 weeks and change in regional tau SUVR over 76 weeks was stronger, with 5 of 9 significant cross-regional coefficients ranging from 0.23 to 0.28. The correlation between change in amyloid over 24, 52, and 76 weeks and change in tau over 76 weeks are presented in eFigure 3C-D in Supplement 2. The correlations between amyloid change at 52 weeks and tau change at 76 weeks were significant for all 9 cross-regional coefficients (eFigure 3D in Supplement 2). There were fewer significant correlations between amyloid change at 76 weeks and tau change at 76 weeks (eFigure 3D in Supplement 2).

Mediation Model Results

The association of amyloid and tau change was additionally explored (eFigure 4 in Supplement 2). Treatment with donanemab showed that there was a significant effect driving amyloid reduction with a stronger association earlier rather than later. For amyloid change from 0 to 24 weeks, 24 to 52 weeks, and 52 to 76 weeks, the regression coefficients were −0.81, −0.60, and −0.20, respectively. Additionally, early amyloid reduction appeared to have a significant correlation with reduction in AD signature-weighted neocortical tau. The 24-week amyloid-reduction path captures approximately 62% of the total effects of treatment on amyloid change on tau in this mediation model.

Amyloid Levels and Cognition

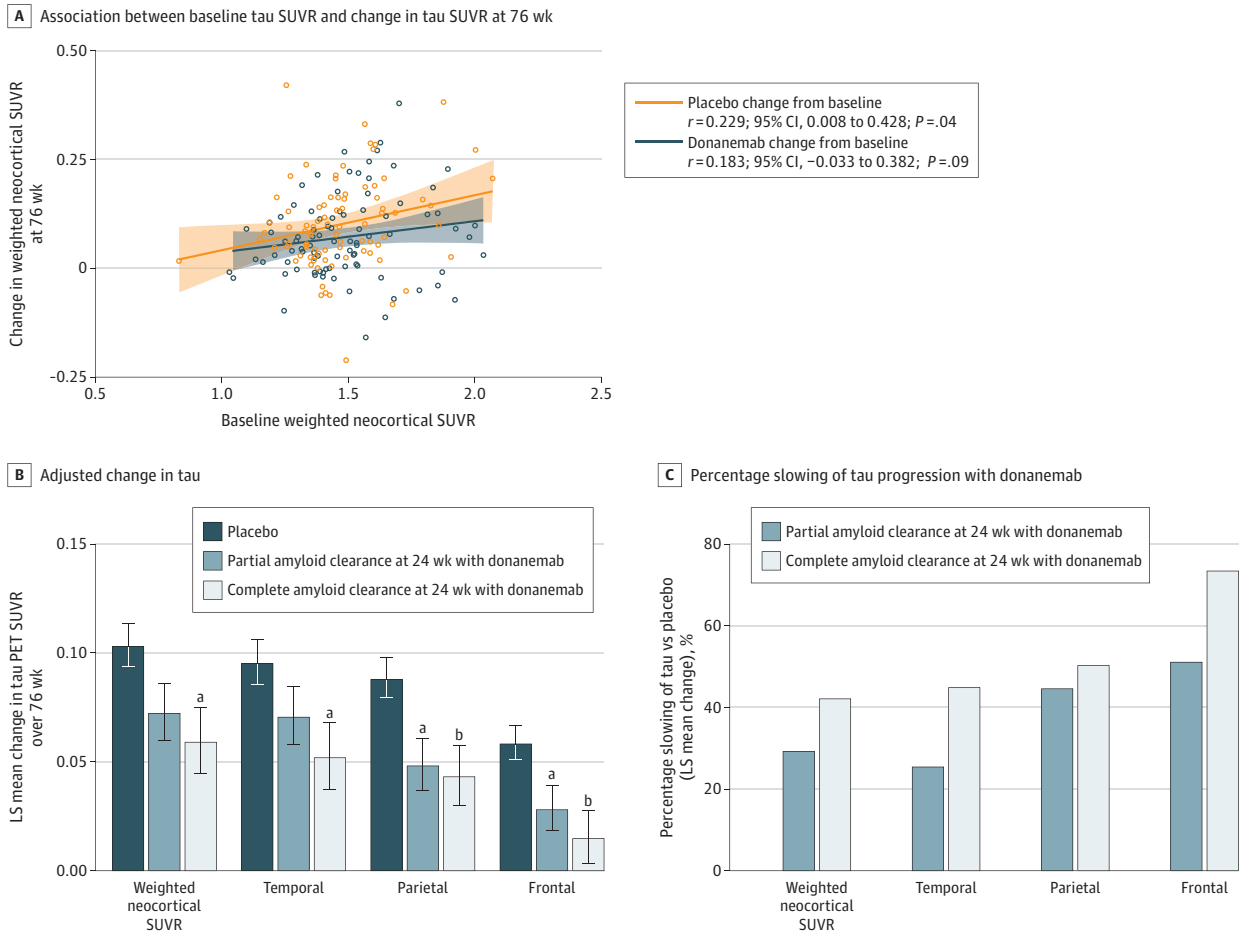
In the overall participant population, a disease-progression model was developed to describe the association between amyloid reduction and change in the rate of disease progression. The model was able to adequately predict observed iADRS values and replicate the time course and distribution of iADRS scores observed over the course of TRAILBLAZER-ALZ (**Figure 5**). The model predicted that a maximum percentage decrease in amyloid plaque from baseline would significantly reduce the rate of disease progression, as measured by the iADRS scale (23%; 95% CI, 3%-40%; $P < .001$) (Figure 5A). However, this effect is only significant in *APOE* ε4 carriers (44%; 95% CI, 24%-59%; $P < .001$) (Figure 5B). The model shows no effect for noncarriers of *APOE* ε4 (Figure 5B).

Discussion

In these post hoc TRAILBLAZER-ALZ analyses, we elaborated on previously reported[2] donanemab-induced amyloid reduction and change in tau as measured using amyloid and tau PET, respectively. We used correlations and logistic regressions as well as 3 modeling approaches to reveal potential associations between amyloid reduction and both tau pathology and clinical outcomes.

The TRAILBLAZER-ALZ randomized clinical trial was designed to achieve rapid amyloid clearance, and results from the current analysis revealed that those participants with higher baseline amyloid levels experienced a greater magnitude of change over 24 weeks, and those with lower baseline amyloid levels were more likely to achieve complete amyloid clearance. These results predict that those with lower baseline amyloid levels are more likely to be able to stop donanemab treatment sooner. Once complete amyloid clearance was achieved and participants switched to placebo infusions, plaques did not regrow substantially over 1 year without treatment. The exposure-response model of amyloid plaque level over time suggested that it might take 3.9 years for plaques to reaccumulate to the plaque clearance threshold of 24.1 CL (assumes starting from an 11 CL threshold). The average

Figure 4. Change in Tau Standardized Uptake Value Ratios (SUVRs)



D Region-by-region Spearman correlations between amyloid SUVR and tau SUVR change at 76 wk among those treated with donanemab

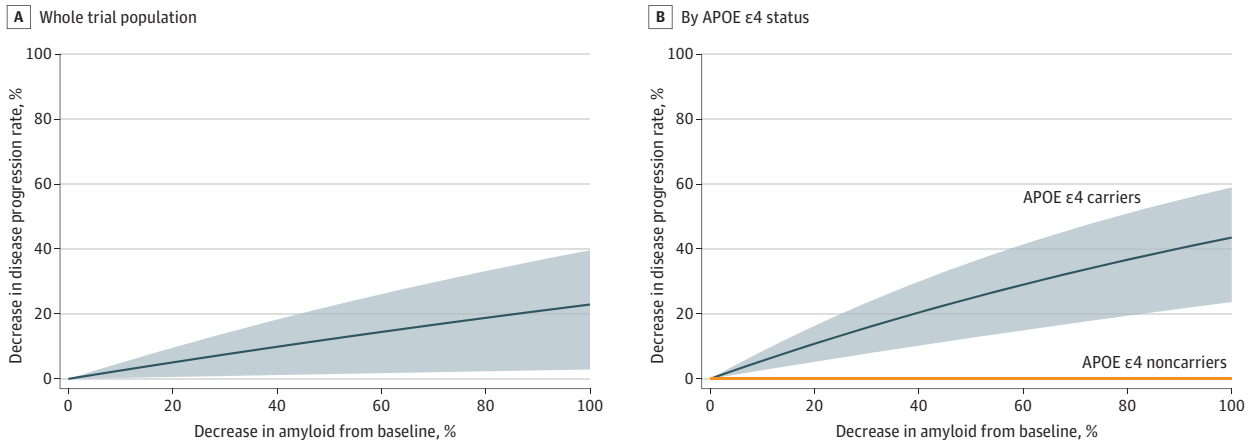
	Brain region	Amyloid level at 24 wk			Change in amyloid SUVR at 24 wk			Percentage change in amyloid SUVR at 24 wk		
		Frontal	Lateral temporal	Parietal	Frontal	Lateral temporal	Parietal	Frontal	Lateral temporal	Parietal
Tau change at 76 wk	Frontal	0.22[a]	0.06	0.08	0.20	0.12	0.17	0.23[a]	0.14	0.19
	Lateral temporal	0.22[a]	0.19	0.13	0.22[a]	0.13	0.14	0.24[a]	0.18	0.18
	Parietal	0.19	0.14	0.15	0.26[a]	0.24[a]	0.24[a]	0.27[a]	0.27[a]	0.28[b]

A, Association between baseline tau SUVR and change in tau SUVR at 76 weeks. Mean (SD) values at baseline and 76 weeks are shown in eTable 2 in Supplement 2. B, Adjusted change in tau was measured using Alzheimer disease (AD) signature-weighted neocortical SUVR and 3 regional SUVRs. Bars show mean (SE) and significance relative to placebo. Baseline characteristics for partial and complete amyloid clearance subgroups are shown in eTable 1 in Supplement 2 (no significant difference between baseline tau SUVR was observed). C, Percentage slowing of tau progression with donanemab was measured using AD signature-weighted neocortical SUVR and 3 regional SUVRs. D, Significant region-by-region Spearman correlations between amyloid SUVR metrics (absolute level at 24 weeks, change from baseline to 24 weeks, and percentage change from baseline to 24 weeks) and tau SUVR change at 76 weeks in donanemab-treated participants are indicated in blue. All participants shown underwent flortaucipir PET scans at baseline and 76 weeks. Participants receiving donanemab are designated as having partial or complete amyloid clearance based on the amyloid plaque level at 24 weeks. Complete amyloid clearance defined as less than 24.1 centiloids (CL); partial amyloid clearance is defined as 24.1 CL or greater. Tau level was measured using SUVR with modified cerebellar gray matter as a reference region. LS indicates least squares; PET, positron emission tomography.

[a] *P* value < .05.

[b] *P* value < .01.

Figure 5. Modeled Association Between Change in Amyloid Plaque and Disease Progression Rate



Disease progression model-predicted percentage decrease in disease progression rate (measured by integrated Alzheimer Disease Rating Scale) (eMethods in Supplement 2), as a result of percentage decrease in amyloid plaque from baseline. With donanemab treatment, participants who achieve low amyloid plaque levels (simulated 100% decrease in amyloid from baseline) will experience a subsequent decrease in disease progression rate. Associations between amyloid positron emission tomography (PET; exposure-response model based on 304 participants from NCT02624778 and TRAILBLAZER-ALZ) and disease progression (model based on 187 carriers and 68 noncarriers from TRAILBLAZER-ALZ as the iADRS was not assessed in NCT02624778) are shown for the whole population (A) and in participants by apolipoprotein E (*APOE*) ε4 carrier genotype (B). The genotype of 1 participant was unknown. Lines represent means and 95% CIs (shaded). CI cannot be calculated in this model for the no effect in noncarriers.

predicted rate of amyloid reaccumulation over this period was approximately 3.4 CL per year. This finding was almost identical to the approximately 3.3 CL per year estimated rate of the natural amyloid accumulation model (an average of 6.4 years is needed for the amyloid level to increase from 4 CL to 25 CL).[24]

The discovered association between baseline amyloid level and change in amyloid (Figure 3A) suggests that the percentage change in amyloid is an important characteristic of amyloid reduction. Therefore, we used percentage change when modeling the association between amyloid reduction and clinical decline (Figure 5). The disease-progression model uses all of the available time-course data and shows a highly significant predicted association between percentage amyloid plaque reduction from baseline and slowing of cognitive decline for *APOE* ε4 carriers. Lack of effect modeled for ε4 noncarriers may be attributable to several factors, such as the relatively few noncarriers (68 noncarriers) in TRAILBLAZER-ALZ[2] or pharmacogenomic differences in treatment response.

Another important parameter for patients with AD is an early crossing of an amyloid clearance threshold. Participants who had complete plaque clearance at 24 weeks showed a greater slowing of tau accumulation over 18 months than participants who did not reach the 24.1 CL threshold by week 24. Importantly, the donanemab-treated participants who achieved complete clearance of amyloid plaque by 24 weeks had nearly complete abrogation of tau progression in some frontal regions (eFigure 3 in Supplement 2). This reduced progression strengthens the hypothesis of an amyloid-mediated tauopathy and has important implications for antiamyloid treatments because it has previously been shown that the amount of brain tau pathology predicts subsequent cognitive decline.[25-28] Because the cohort with complete plaque clearance at week 24 had slightly but significantly lower amyloid plaque at baseline, it was possible that these participants had milder disease at baseline. To evaluate this possibility, we compared baseline characteristics for these 2 cohorts. As shown in eTable 1 in Supplement 2, the participants with complete plaque clearance were slightly older than the participants with partial clearance, and as noted previously, had lower amyloid burden, but otherwise there were no significant differences between the groups. Thus, a parsimonious interpretation of the results in Figure 4 and eFigure 3 in Supplement 2 is that early reduction of amyloid reduced the proportion of time within the 18-month study during which amyloid plaque was able to drive downstream pathology such as tau accumulation.

Results of the current study demonstrated the usefulness of multiregional approaches where the target brain regions are ordered according to the pathologic sequence of tau progression. In this respect, we showed the regional tau PET data arranged according to lobar classification and event-based modeling. These 2 multiregional schemes suggested a slowing of tau accumulation with donanemab compared with placebo, with less accumulation in the brain regions identified later in the tau pathologic sequence.

Limitations

There were several limitations to this study. First, these results are from exploratory, post hoc analyses. Second, analyses of postrandomization events have a risk for bias, and interpretation should be cautious. However, new trials and planned analyses will be able to ascertain whether these findings are robust. Third, these exploratory analyses do not control for multiplicity; therefore, inflated type I error likely exists. Fourth, these data come from a trial that is relatively small compared with larger phase 3 studies. Confirmation of these

findings is critical in other studies with robust amyloid lowering. Fifth, the trial population has less racial and ethnic diversity compared with the target population; therefore, any differences in response to treatment are not reflected. Sixth, the single postrandomization tau PET scan limits analysis of this outcome to completers only. In addition, the understanding of the optimal method for assessing tau changes requires further investigation, as neither the Tau^{IQ} algorithm[5] nor the AD signature-weighted neocortical SUVR[7] with respect to PERSI[29] showed significant response to donanemab. Seventh, the disease-progression model includes inherent assumptions (eMethods in Supplement 2). Eighth, the modeling results can be considered as hypothesis generating, and data from other trials will be important to confirm revealed trends.

Conclusions

Overall, results of this post hoc analysis of the TRAILBLAZER-ALZ randomized clinical trial have shown that complete amyloid plaque clearance achieved with donanemab was associated with lower amyloid at baseline and slower disease progression at 76 weeks as determined by tau accumulation and clinical decline. These results underscore the importance of amyloid plaques in AD and understanding amyloid status for treatment decisions. Data from other trials, eg, TRAILBLAZER-EXT,[30] TRAILBLAZER-ALZ 2,[31] and TRAILBLAZER-ALZ 4,[32] will be important to confirm the aforementioned observations.

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