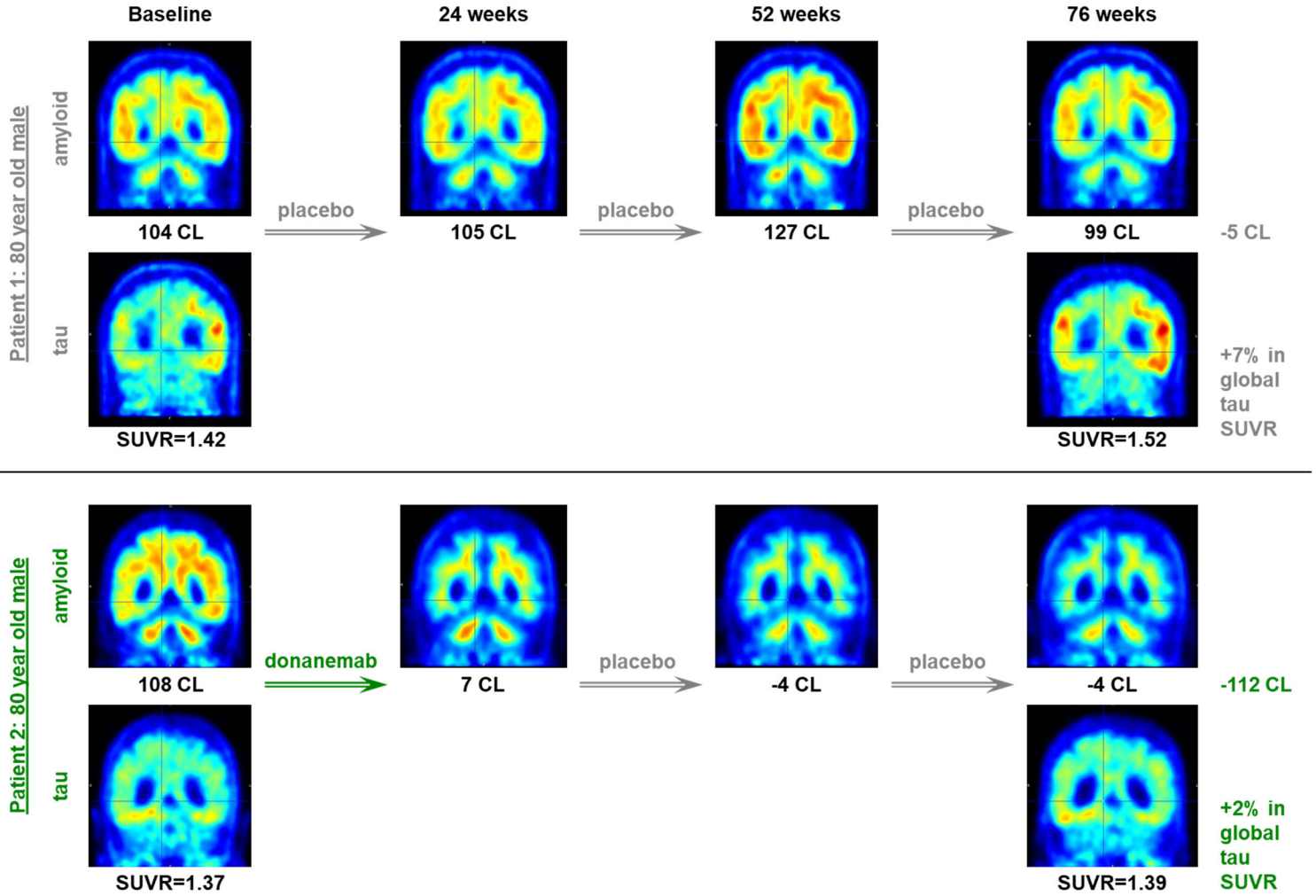
Supplementary Online Content

Shcherbinin S, Evans CD, Lu M, et al. Association of amyloid reduction after donanemab treatment with tau pathology and clinical outcomes: the TRAILBLAZER-ALZ randomized clinical trial. *JAMA Neurol*. Published online September 12, 2022. doi:10.1001/jamaneurol.2022.2793

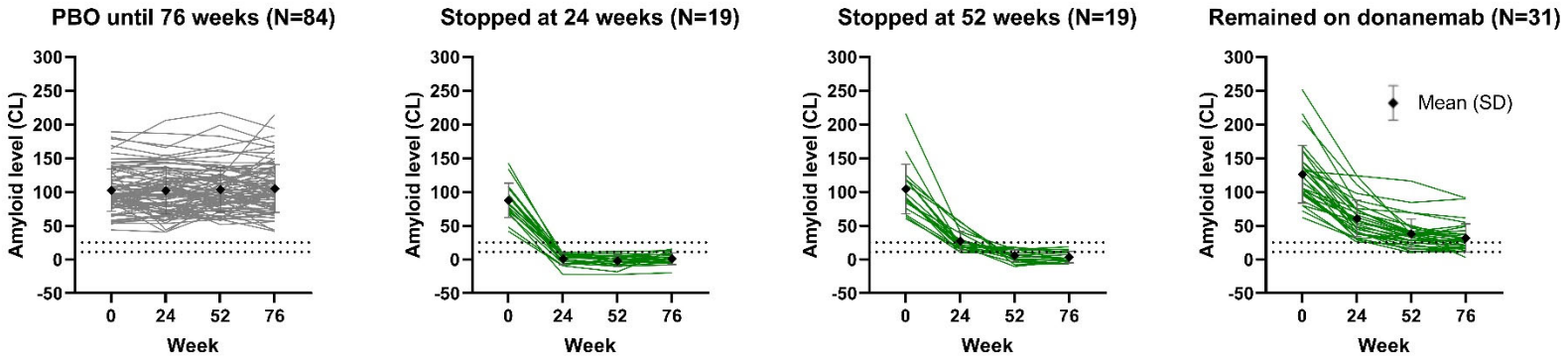
This supplementary material has been provided by the authors to give readers additional information about their work.

eFigure 1. Representative Amyloid and Tau PET Scans Showing Changes After Placebo and Donanemab Treatment Over the Course of 76 Weeks



Note: Tau level is measured using an AD-signature weighted neocortical SUVR with respect to cerebellum gray as a reference.

eFigure 2. Individual Participant Trajectories Showing Amyloid Levels Are Maintained Once Donanemab Treatment Is Discontinued

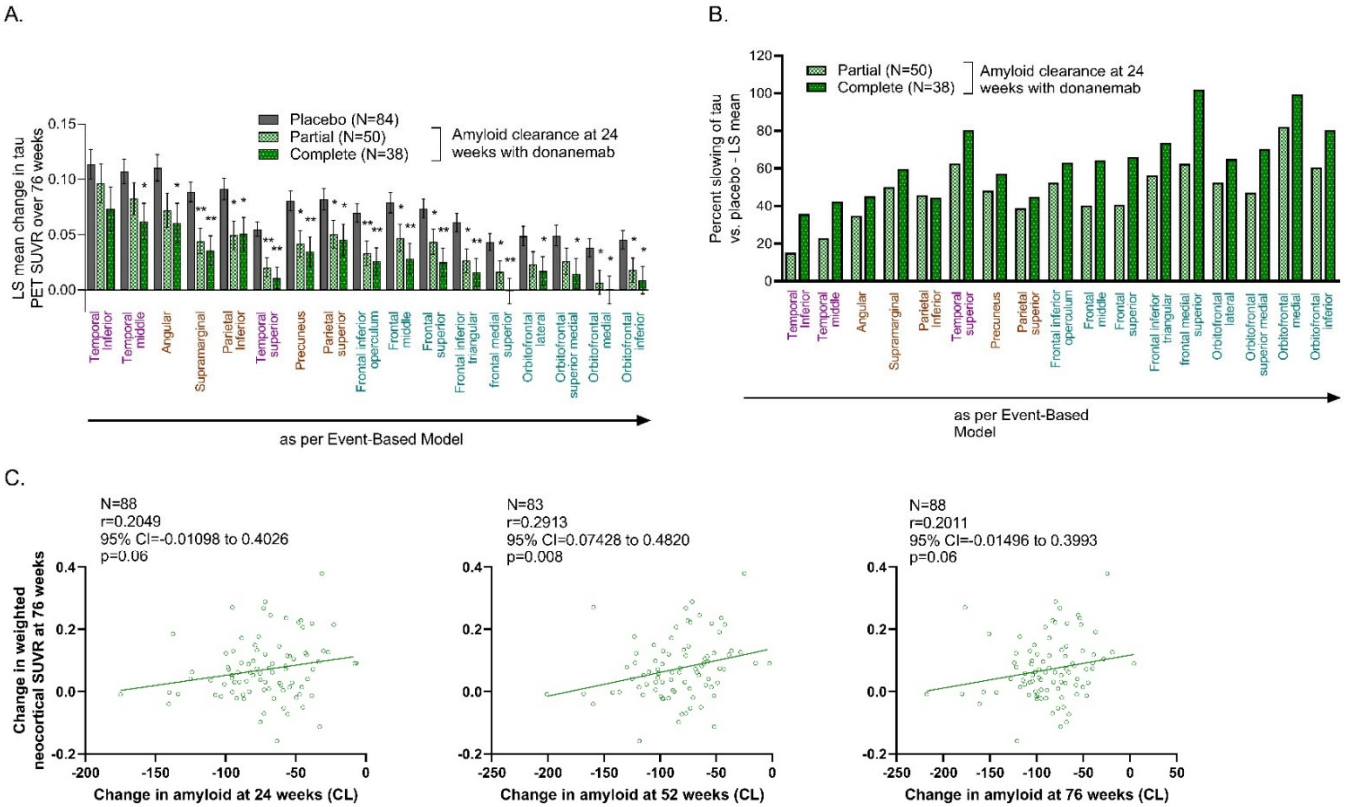


At 24 weeks, 19 participants were switched to placebo; at 52 weeks, 19 participants were switched to placebo, and 31 remained on donanemab until end of study. The 11 and 25 CL thresholds are indicated with dotted lines. The mean (black diamonds) and standard deviation (error bars) can also be found in eTable 2.

Notes: Only participants with interpretable amyloid scans taken at all timepoints were included in this dose-dependent subgroup analysis. Note, follow-up florbetapir scans were processed individually when the dose change decision was being made during the trial. The longitudinal trajectories presented in this manuscript and eFigure 3 were generated using longitudinal pipeline, where follow-up images were spatially normalized to the corresponding baseline scan before quantification.

CL = Centiloids

eFigure 3. LS Mean Change and Percentage Slowing of Tau and Regional Tau and Amyloid Correlations

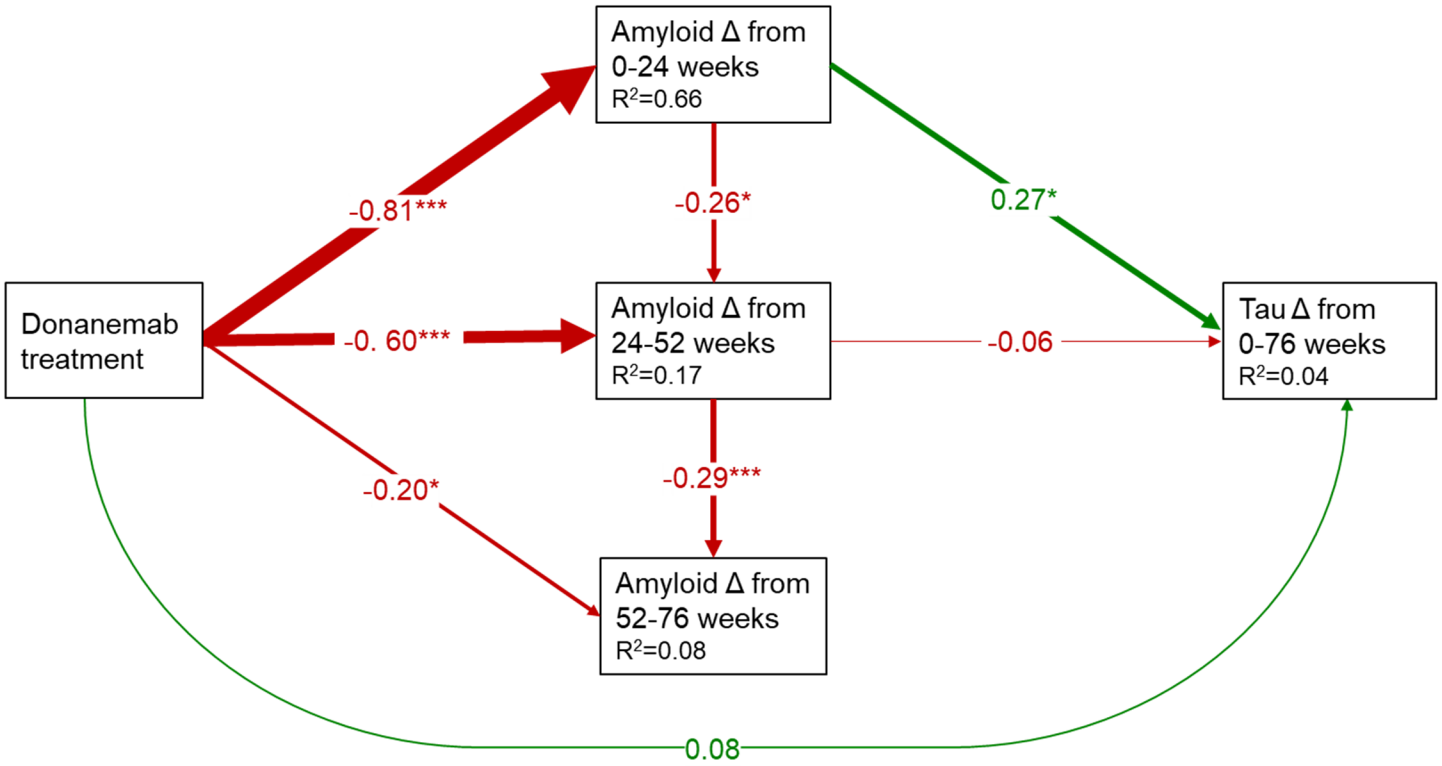


D.

		Change in amyloid SUVR at 52 weeks			Change in amyloid SUVR at 76 weeks		
	Brain Region	Frontal	Lateral temporal	Parietal	Frontal	Lateral temporal	Parietal
Tau change at 76 weeks	Frontal	0.27*	0.26*	0.25*	0.18	0.19	0.16
	Lateral temporal	0.32**	0.26*	0.24*	0.21*	0.16	0.15
	Parietal	0.27*	0.29**	0.26*	0.18	0.22*	0.18

(A) Donanemab decreased tau progression in specific regions of interest. Bars show mean +/- standard error. * *P*-value <.05; ** *P*-value <.01; Number of scans and baseline characteristics for complete and partial clearance subgroups are shown in eTable 1.
(B) Generally, percent slowing of tau progression with donanemab was greater in participants with complete amyloid clearance than those with partial amyloid clearance at 24 weeks.
(C) Scatter plots showing the relationship between change in amyloid at 24, 52 and 76 weeks and change in tau at 76 weeks. Baseline characteristics for complete and partial clearance subgroups are shown in eTable 2.
(D) Tau SUVR change at 76 weeks in donanemab-treated participants was significantly correlated with amyloid change at 52 weeks in all 9 cross-sections and in 2 of 9 cross-sections with amyloid change at 76 weeks.
Footnote: 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 <24.1 CL; Partial amyloid clearance defined as ≥24.1 CL. Cortical tau level was measured using regional tau SUVR with modified cerebellar gray matter as a reference region.
CL = Centiloids; LS = least squares; PET = positron emission tomography; SUVR = standardized uptake value ratio; **P*<.05; ***P*<.01 vs. placebo

eFigure 4. Mediation Model



Mediation model using the whole population showing the paths to Tau AD-signature weighted neocortical SUVR with the regression coefficients shown as values on the vectors and the R^2 values from the 4 regression analyses are shown in the boxes. Treatment with donanemab shows that there is significant effect driving amyloid reduction with a stronger earlier relationship than later relationship. Notes: The regression coefficient from the 52–76-week amyloid change to 0-76-week tau change was -0.00. Test of fit: Root Mean Square Error of Approximation=0.034 (<0.05), Comparative fit index=0.999 and Tucker-Lewis Index=0.992 (>0.95), Standardized Root Mean Square Residual=0.013 (<0.05)

Abbreviations: amyloid Δ = amyloid PET SUVR change since previous timepoint; tau Δ = change in AD-signature weighted neocortical tau SUVR since baselin

eTable 1. Characteristics of Amyloid Subgroups

	Placebo	Overall donanemab population	Complete clearance at week 24 with donanemab	Partial clearance at week 24 with donanemab	Partial vs complete clearance *P*-value
Baseline characteristics					
Age - n, mean (SD)	120, 75.29 (5.438)	115, 75.05 (5.555)	46, 76.78 (5.168)	69, 73.90 (5.539)	.006
Amyloid CL- n, mean (SD)	112, 103.09 (33.841)	115, 107.56 (34.030)	46, 92.83 (28.696)	69, 117.38 (33.939) §	<.001
AD-signature weighted neocortical SUVR - n, mean (SD)	113, 1.48 (0.210)	112, 1.50 (0.243)	45, 1.51 (0.263)	67, 1.49 (0.230)	ns
MMSE- n, mean (SD)	115, 23.77 (2.878)	23.52 (3.033)	44, 23.55 (3.076)	67, 23.51 (3.027)	ns
ADAS-Cog- n, mean (SD)	120, 27.53 (7.553)	115, 27.81 (7.762)	46, 28.41 (8.323)	69, 27.41 (7.399)	ns
iADRS- n, mean (SD)	120, 106.06 (13.050)	115, 106.31 (12.470)	46, 104.15 (12.887)	69, 107.75 (12.063)	ns
APOE-ε4					
Carriers - n, (%)	88 (73.9)	85 (73.9)	36 (78.3)	49 (71.0)	ns
Noncarriers - n, (%)	31 (26.1)	30 (26.1)	10 (21.7)	20 (29.0)	
LS mean change in tau SUVR at week 76, cerebellar gray as a reference region n, mean (SE)					
AD-signature weighted neocortical SUVR	84, 0.104 (0.0100)	89, 0.069 (0.0974) †	38, 0.0598 (0.0150) †	50, 0.0731 (0.0131)	ns
Occipital SUVR	84, 0.075 (0.0089)	89, 0.059 (0.0087)	38, 0.053 (0.0132)	50, 0.059 (0.0115)	ns
Lateral temporal SUVR	84, 0.096 (0.0103)	89, 0.064 (0.0103) †	38, 0.0527 (0.0153) †	50, 0.0713 (0.0134)	ns
Parietal SUVR	84, 0.089 (0.0092)	89, 0.048 (0.0089) §	38, 0.0439 (0.0137) §	50, 0.0489 (0.0121) †	ns
Frontal SUVR	84, 0.059 (0.0080)	89, 0.023 (0.0078) §	38, 0.0156 (0.0120) §	50, 0.0288 (0.0105) †	ns

AD = Alzheimer's Disease; ADAS-Cog=Alzheimer's Disease Assessment Scale; iADRS = Integrated AD Rating Scale; CL = Centiloids; LS = Least Squares; MMSE = Mini–Mental State Examination; n = Number of participants; PET = positron emission tomography; SUVR = standardized uptake value ratio with cerebellar gray as a reference; Only participants with follow-up PET scans are included

**P*<.001 vs PBO

§*P*<.01 vs PBO

†*P*<.05 vs PBO

Note: For comparisons of baseline characteristics for continuous variables, *P*-values are from two sample t-test; for categorical variables, *P*-values are from Fisher's exact test. Analysis of covariance was used for comparisons of LS mean change.

eTable 2. Amyloid and Tau Across Subgroups at All Time Points Assessed

	Placebo	Overall donanemab population	Complete clearance at week 24 with donanemab	Partial clearance at week 24 with donanemab	Partial vs complete clearance *P*-value
Amyloid (CL) - n, mean (SD)					
Week 0 (baseline)	112, 103.09 (33.841)	115, 107.56 (34.030)	46, 92.83 (28.696)	69, 117.38 (33.939) §	<.001
Week 24	111, 102.08 (36.607)	115, 37.07 (30.934)*	46, 7.70 (10.849)*	69, 56.65 (23.527)*	<.001
Week 52	91, 102.97 (32.818)	91, 24.10 (29.041)*	38, 4.28 (11.543)*	53, 38.32 (29.528)*	<.001
Week 76	91, 103.86 (35.046)	89, 20.50 (27.982)*	39, 4.78 (12.235)*	50, 32.76 (30.662)*	<.001
AD-signature weighted neocortical SUVR- n, mean (SD)					
Week 0- n, mean (SD)	113, 1.48 (0.210)	112, 1.50 (0.243)	45, 1.51 (0.263)	67, 1.49 (0.230)	ns
Week 76- n, mean (SD)	84, 1.57 (0.245)	88, 1.56 (0.256)	38, 1.53 (0.251)	50, 1.58 (0.260)	ns

AD=Alzheimer's Disease; CL = Centiloids; n=Number of participants; SD = standard deviation; SUVR = standardized uptake value ratio

*P<.001 vs PBO

§P<.01 vs PBO

Note: Only donanemab-treated participants with follow-up PET scans at week 24 are included in the donanemab columns. For continuous variables, P-values are from two-sample t-test.

eTable 3. Regional Tau With Comparison of Changes Across Subgroups

	Placebo	Complete clearance at week 24 with donanemab	Partial clearance at week 24 with donanemab
FRONTAL (CC) SUVR			
Baseline: N, Mean (SD)	84, 1.1739 (0.1667)	38, 1.1389 (0.1327)	50, 1.1777 (0.1888)
18 Months: N, Mean (SD)	84, 1.2328 (0.2174)	38, 1.1455 (0.1471)	50, 1.2134 (0.2339)
Straight Change at 18 Months: N, Mean (SD)	84, 0.0589 (0.0831)	38, 0.0067 (0.0558)	50, 0.0357 (0.0909)
LS Mean Change (SE)	0.0590 (0.0080)	0.0156 (0.0120)	0.0288 (0.0105)
LS Mean Diff (95% CI) vs. placebo		0.0434 (0.0150, 0.0719)	0.0302 (0.0041, 0.0564)
LS Mean Diff (95% CI) vs. Complete clearance			-0.0132 (-0.0450, 0.0185)
P-value (vs. placebo)		0.003	0.02
P-value (vs complete clearance)			0.41
LATERAL TEMPORAL (CC) SUVR			
Baseline: N, Mean (SD)	84, 1.4560 (0.1920)	38, 1.4730 (0.2260)	50, 1.4874 (0.2351)
18 Months: N, Mean (SD)	84, 1.5490 (0.2320)	38, 1.5183 (0.2503)	50, 1.5694 (0.2831)
Straight Change at 18 Months: N, Mean (SD)	84, 0.0930 (0.1016)	38, 0.0453 (0.0923)	50, 0.0820 (0.1047)
LS Mean Change (SE)	0.0960 (0.0103)	0.0527 (0.0153)	0.0713 (0.0134)
LS Mean Diff (95% CI) vs. placebo		0.0433 (0.0070, 0.0796)	0.0247 (-0.0088, 0.0582)
LS Mean Diff (95% CI) vs. Complete clearance			-0.0186 (-0.0592, 0.0219)
P-value (vs. placebo)		.02	.15
P-value (vs complete clearance)			.37
AD-signature weighted neocortical SUVR			
Baseline: N, Mean (SD)	84, 1.4685 (0.1978)	38, 1.4791 (0.2258)	50, 1.4951 (0.2193)
18 Months: N, Mean (SD)	84, 1.5692 (0.2446)	38, 1.5309 (0.2511)	50, 1.5794 (0.2601)
Straight Change at 18 Months: N, Mean (SD)	84, 0.1008 (0.1040)	38, 0.0518 (0.0839)	50, 0.0842 (0.1026)
LS Mean Change (SE)	0.1037 (0.0100)	0.0598 (0.0150)	0.0731 (0.0131)
LS Mean Diff (95% CI) vs. placebo		0.0439 (0.0084, 0.0795)	0.0306 (-0.0022, 0.0634)
LS Mean Diff (95% CI) vs. Complete clearance			-0.0133 (-0.0530, 0.0263)
P-value (vs. placebo)		.02	.07
P-value (vs complete clearance)			.51
PARIETAL (CC) SUVR			
Baseline: N, Mean (SD)	84, 1.2529 (0.1853)	38, 1.2411 (0.2087)	50, 1.3035 (0.2318)
18 Months: N, Mean (SD)	84, 1.3388 (0.2394)	38, 1.2761 (0.2335)	50, 1.3637 (0.2514)
Straight Change at 18 Months: N, Mean (SD)	84, 0.0859 (0.1015)	38, 0.0350 (0.0664)	50, 0.0602 (0.0881)
LS Mean Change (SE)	0.0886 (0.0092)	0.0439 (0.0137)	0.0489 (0.0121)
LS Mean Diff (95% CI) vs. placebo		0.0447 (0.0122, 0.0773)	0.0396 (0.0096, 0.0697)
LS Mean Diff (95% CI) vs. Complete clearance			-0.0051 (-0.0415, 0.0314)
P-value (vs. placebo)		.007	.01
P-value (vs complete clearance)			.78

eMethods

Participants and study design

TRAILBLAZER-ALZ (NCT03367403) was conducted according to Good Clinical Practice and adhered to international ethics guidelines, including the Declaration of Helsinki and the Council for International Organizations of Medical Sciences International Ethical Guidelines. The study was reviewed and approved by appropriate local ethics committees, and written informed consent was obtaining from study participants.

The study originally included a donanemab + LY3202626 (an inhibitor of ß-site amyloid precursor protein cleaving enzyme 1) combination group, which was discontinued early and was not included in analyses (see eFigure 1).

Information collected from TRAILBLAZER-ALZ included sex, age, race, ethnicity, weight, height, body mass index, country, acetyl-cholinesterase-inhibitor, and memantine use at baseline, job class, first-degree relatives with AD, years of education, apolipoprotein E4 (APOE-ε4) genotype, smoking history, alcohol consumption, baseline amyloid, and other baseline disease severity parameters. Participants self-reported based on multiple choice selection of American Indian or Alaska Native, Asian, Black or African American, Multiple, White, and Hispanic or Latino or not as for Federal reporting purposes (https://www.fda.gov/media/75453/download). Demographic information not presented here was reported elsewhere[1] or out of scope.

Florbetapir PET

Florbetapir PET scans (20-minute scans 50 minutes post injection of 10 mCi [370MBq] florbetapir) were performed at baseline and at 24, 52, and 76 weeks after the first treatment to quantitatively estimate change in amyloid plaques. When making a dose change decision at 24 and 52 weeks, images were spatially registered to the brain space and quantified. When quantitatively assessing longitudinal change in amyloid level at the end of the trial, follow-up images were first spatially registered to the corresponding baseline image. A composite SUVR with 6 predetermined target cortical regions and whole cerebellum as a reference region was calculated[2] and then converted to CL units[3].

Flortaucipir PET

Flortaucipir PET scans (30-minute scans 75 minutes post injection of 10 mCi [370MBq] flortaucipir) were collected at baseline and after 76 weeks to quantitatively assess longitudinal change in tau burden.

Event-based model

The Event-Based Model[4,5] is a fully data-driven method to temporally order brain regions according to the expected time until significant tau accumulation. The EBM treats each brain region as either “tau unburdened” or “tau burdened”, where Gaussian probability density functions govern the distribution of tau measurements under these two settings. A brain region experiences an event when it switches from normal to abnormal tau levels and ordering these events defines the sequence. As such, the sequence is the primary parameter of the model to be learned from the regional tau SUVR dataset.

We used independent dataset to AAL atlas regions into a pathologic spreading sequence using an event-based model. In application, we run the EBM for 250000 iterations, where each step the algorithm swaps the positions of two brain regions and accepts the new sequence if the data

fit improves. Seventeen AAL regions belonging to temporal, parietal, and frontal lobes were included in eFig.4A and 4B.

Mediation model

A mediation model was constructed using the laavan package in R to assess the different pathways that donanemab treatment affected change in tau PET (AD-signature weighted neocortical SUVR) at 76 weeks. This analysis was restricted to study participants with week 76 assessments of tau PET and amyloid PET assessments at weeks 24, 52, and 76. Because the amount of amyloid clearance at months 6, 12 and 18 could differentially impact tau PET change from baseline scores at week 76, participants in the mediation analysis were required to have amyloid PET data at weeks 24 and 52. The mediation model included variables for the amount of amyloid PET change from baseline to week 24, the amount of amyloid PET change from week 24 to week 52, and the amount of amyloid PET change from week 52 to week 76. Five regression equations were constructed for this mediation model:

TAU18 ~ TRT + FBP24 + FBP52 + FBP76

FBP24 ~ TRT

FBP52 ~ TRT + FBP24

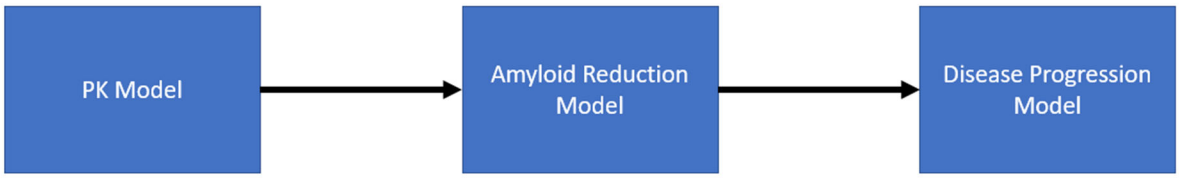
FBP76 ~ TRT+ FBP52

Where TRT = randomized treatment (donanemab=1/placebo=0), FBP24 = change from baseline to week 24 in amyloid PET, FBP52 = change from week 24 to week 52 in amyloid PET, FBP76 = change from week 52 to week 76 in amyloid PET, and TAU76 = change from baseline to week 76 in tau PET.

Development of PK/PD models

A PK/PD modelling approach was used to explore the effect of donanemab on amyloid plaque, and to explore the potential relationship between amyloid reduction and change in Alzheimer's disease progression. These analyses were exploratory in nature but, followed a pre-specified population analysis plan that was finalized before the completion of the TRAILBLAZER-ALZ study. Models were developed in a stepwise fashion, with the PK model first developed, followed by the amyloid reduction model, and finally using these earlier models to develop the disease progression model (Figure S.1). All modelling was conducted using NONMEM 7.4.2 (Icon Development Systems, Hanover, MA), Perl Speaks NONMEM (PsN) v4.8[6], and R v3.6[7].

Figure S.1. Schematic of model development process



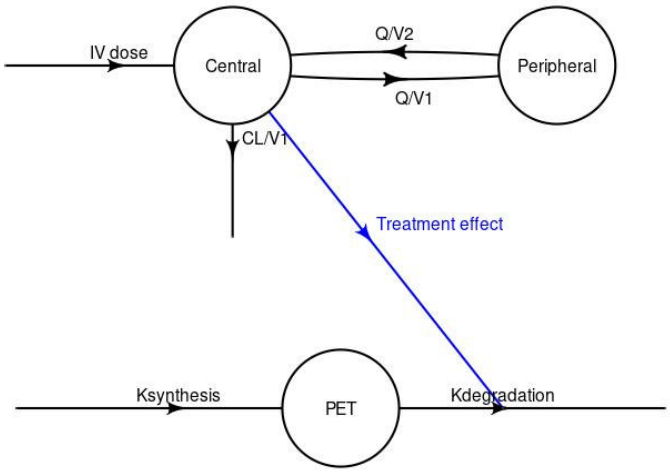
Amyloid reduction (exposure-response) model

The PK model was developed using observed serum donanemab concentrations along with recorded dosing and sample time information. The concentration data were used to fit a 2-compartment model parameterized in terms of clearance, central (serum) and peripheral volumes of distribution, and intercompartmental clearance. The base model included inter-subject variability terms on central volume and clearance. Based on the known properties of monoclonal antibodies, the effect of body weight on clearance and volume of distribution was prespecified using typical allometric scaling[8,9]. A stepwise covariate modelling approach (as implemented by PsN) was used to explore the potential significance of other prespecified covariates of interest, including age, gender, APOE-ε4 carrier status, race, ethnicity, and ADA titer. A p-value of 0.01 was used during the forwards inclusion step and a p-value of 0.001 was used to retain covariates during the backwards elimination step. Of the covariates tested, only the effect of body weight on clearance and central volume of distribution, and ADA titer on clearance remained in final model. The overall adequacy of the model was assessed using a visual predictive check with 500 simulations, and the precision of the model parameters were assessed using a bootstrap analysis with 500 re-samplings.

The amyloid reduction model was developed using observed amyloid plaque values, as obtained using Florbetapir F18 PET tracer, expressed in Centiloid units. The data used in this analysis included all participants in TRAILBLAZER-ALZ (placebo- and donanemab-treated), as well as data from a previous dose-ranging trial[10] (NCT02624778). As prespecified in the population analysis plan, an indirect response model was fit to the data to describe the change in amyloid plaque load over time (Figure S.2). Model parameters were plaque formation rate (k_{in}), baseline plaque load, and plaque elimination rate (k_{out}). To improve model stability, the assumption was made that plaque levels placebo participants were approximately stable over the course of the trial, and so the plaque formation rate could be calculated as the product of the plaque load and the elimination rate constant at baseline. Donanemab activity was characterized by an increase in k_{out}. The data supported the inclusion of inter-individual variability parameters on baseline amyloid levels and k_{out}. Donanemab exposure for each participant was calculated using individual post-hoc PK parameter estimates as developed by the population PK model. These PK parameter estimates were used to calculate area under the plasma-concentration time curve over a dosing interval (AUC) at steady state, or the donanemab concentration at any particular point during the trial. Several approaches were used to link donanemab exposure to the increase in k_{out}, including linear and Michaelis-Menten type equations. In the final base model, a threshold approach (where donanemab was only active above a certain concentration) was found to provide the lowest objection function value while producing stable parameter estimates. A stepwise covariate search for influential covariates was performed using the SCM algorithm in PsN, testing age, gender, APOE-ε4 carrier status, race, ethnicity, and ADA titer as covariates on baseline amyloid level and k_{out}.For the exposure-amyloid reduction model no statistically significant covariates were found; baseline amyloid plaque was initial condition for PET compartment (see Figure S.2).

Donanemab PK was influenced by body weight and anti-drug antibody (ADA) titer. Time courses of ADA titer and body weight were sampled from the dataset and last-observation-carried-forward (LOCF) applied to replicate the time-varying effect of titer on clearance in the PK model.

Figure S.2. Schematic of the amyloid reduction model.



Display of the dose administered into the central compartment with subsequent distribution into peripheral tissues. Donanemab treatment effect stimulates degradation rate of amyloid plaque.

Abbreviations: CL=clearance, IV=intravenous; Kdegradation=rate of amyloid plaque degeneration; Ksynthesis=rate of amyloid plaque synthesis; PET=positron emission tomography; Q=intercompartment clearance; V1= volume of distribution in central compartment; V2=volume of distribution in peripheral compartment. Treatment effect=donanemab treatment, where donanemab serum concentrations were estimated for each participant using population PK methods and individual post-hoc PK parameter estimates.

The amyloid reduction model (based on 304 participants) was used to evaluate the re-accumulation rate for participants who achieved <11 CL by 24 weeks and then discontinued donanemab treatment. Using the estimated parameters, 1000 participants were simulated to follow dosing treatment regimen, including the potential for down-titration based on Centiloid units at weeks 24 and 52. The simulations used the donanemab population amyloid plaque reduction model.

Disease progression model

A disease progression model for the iADRS scale was developed based upon an approach described in the literature for the ADAS-Cog scale[11]. The advantages of this model were chiefly in the use of beta regression, which better captures the heteroscedasticity of the residual variability in the model as compared to more traditional nonlinear regression techniques. To

develop the model, iADRS scores from all participants in TRAILBLAZER-ALZ were used to fit Richard's logistic function via beta regression. To better test the significance of donanemab concentration and change in amyloid as predictors of change in disease progression, differential equations were used to describe the change in PK, amyloid, and disease progression. All iADRS scores were rescaled to the [0, 1] interval to enable beta regression (Equation 1).

$$iADRS_{scaled} = \left(1 - \frac{iADRS_{observed}}{iADRS_{max}}\right) \qquad (1)$$

The Richard's function was parameterized in terms of intrinsic rate of disease progression (IRATE) and a shape parameter (SH), as shown in Equation 2.

$$\frac{diADRS}{dt} = IRATE \cdot iADRS \cdot (1 - iADRS^{SH}) \qquad (2)$$

Both use of donanemab and the extent of amyloid reduction were tested as covariates on IRATE, and both were statistically significant. The reported model used change in IRATE as a function of amyloid reduction to describe the change in disease progression, as this was aligned with the proposed mechanism of action for donanemab. Change in amyloid was tested as both absolute change, as well as percent change from baseline. The version of the model using percent change from baseline had a slightly lower objective function than the version using absolute change in amyloid level, suggesting a better model fit, and so percent change from baseline was chosen as the factor influencing change in disease progression. The base model also included inter-individual variability terms on baseline. During model development, the shape parameter of the Richard's function could not be estimated with precision. This shape parameter defines an inflection point at which the apparent rate of disease progression (as measured by the clinical scale) begins to decrease. In an analysis of the ADNI dataset, this inflection point was estimated to occur relatively late in the course of the disease (at ADAS-Cog scores around 52). In a disease progression model developed using the iADRS scale with placebo data from over 2400 participants[12], the inflection point was found to occur at around a value of 37, corresponding to a shape parameter of 7.25. This is consistent with the consistent with the relatively late occurrence of the published inflection point[8]. Because the patient population in TRAILBLAZER-ALZ was relatively early in the course of the disease, it was reasonable that the shape parameter reflecting this inflection point could not be estimated with precision. Accordingly, the shape parameter in this model was fixed to the literature value of 7.25.

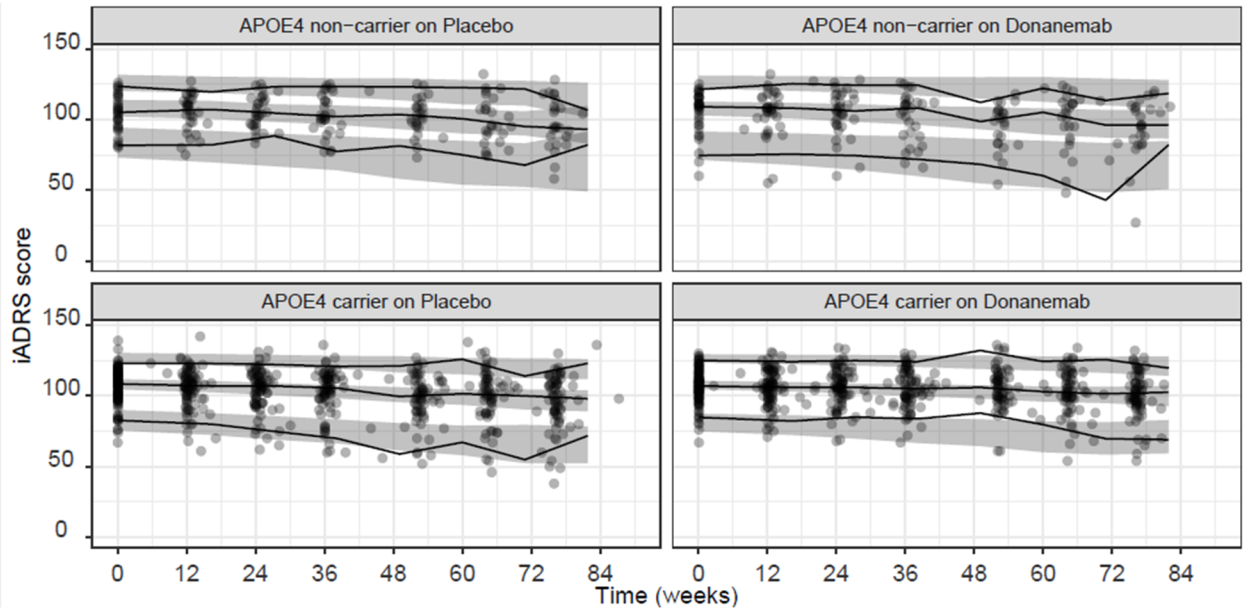
Using stepwise covariate modelling, as implemented in PsN, age, gender, race, APOE-ε4 carrier status, baseline tau and ADA titer were tested as potential covariates on baseline iADRS and IRATE, as well as the effect of donanemab on IRATE. Both for the forward inclusion and backward deletion criteria were p-value<0.001. The effect of APOE-ε4 carrier status was statistically significant in the disease progression model, specifically on the term describing the effect of amyloid reduction on the intrinsic rate of change in disease progression (IRATE). Tested individually, the effect of amyloid reduction on disease progression was only statistically significant in APOE-ε4 carriers. It is unclear whether the lack of a statistically significant effect in APOE-ε4 noncarriers reflects the relatively few noncarriers in TRAILBLAZER-ALZ, a relatively smaller effect in noncarriers, or a combination of the two factors. The effect of amyloid reduction on IRATE was modelled as in Equation 3, where $IRATE_{typical}$ is the typical intrinsic rate of change in disease progression in participants, θamyloid is the parameter describing the effect

of amyloid reduction on IRATE, and AmyloidPC is the percent change in amyloid reduction. The resulting relationship is shown in Figure 5 of the manuscript.

$$\frac{dIRATE}{dt} = IRATE_{typical} \cdot IRATE(t) \cdot (1 - IRATE(t)^{SH}) \cdot e^{(\theta amyloid \cdot AmyloidPC)} \quad (3)$$

Goodness of fit plots were generated using model estimated individual and population predicted iADRS scores and comparing these to the observed values. Standard ordinary residuals were generated following previously described methods[9]. The residual plots (not shown) did not indicate a trend for the individual predicted score and time. Figure S.3 displays the visual predictive check (VPC), which supported the validity of the model. and bootstrap analysis (not shown) indicated that the parameters are well estimated. Model validity was assessed by comparing the 5th, and 95th percentiles of the observations in the actual dataset to their respective model predicted 95% CIs.

Figure S.3. Visual predictive check for amyloid PET model linked to iADRS



Disease progression model (gray shaded areas) adequately describes the observed cognitive scores (iADRS scale) over time for placebo and donanemab treated participants.

Abbreviations: iADRS= Integrated Alzheimer's Disease Rating Scale PET= positron emission tomography. The points are the observed data. The lines are the 5th, 50th and 95th percentiles of the observed data. The shaded areas are the model-predicted 95th confidence interval of the corresponding percentiles.

Limitations regarding the disease progression model are that no drop out model was used to account for missing data and that normal distribution was assumed for inter-participant variability of the intrinsic rate of disease progression. There was no additional information to inform pattern for drop out model and normal distribution is typically followed for rates unless there is data to support alternative distribution assumption.

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