

Post-hoc analyses of amyloid reduction after one year of treatment with donanemab using clinical trial data: prediction of amyloid clearance and association with downstream measurements

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Supplement

Figure S1: Change from baseline in regional tau PET in donanemab-treated subgroups compared with corresponding mPBO subgroups at 76 weeks

Data are shown as the least-squares mean (SE) change from baseline. Note that tau PET signal here is measured using the standardized uptake value ratio with cerebellar crus as the reference region. ** $p < 0.01$ vs mPBO.

Abbreviations: AC_{W52}, amyloid < 24.1 CL at week 52; mPBO, matched placebo; NAC_{W52}, amyloid ≥ 24.1 CL at week 52; PET, positron emission tomography; SE, standard error.

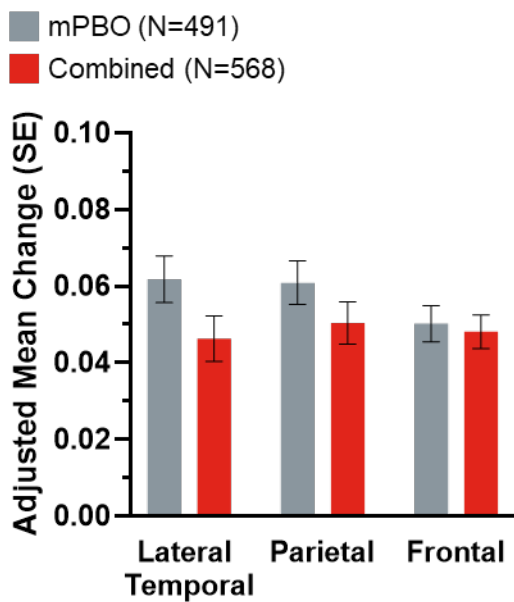
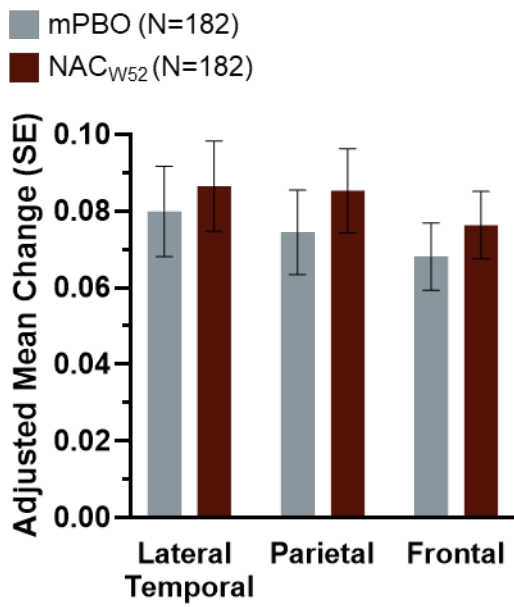
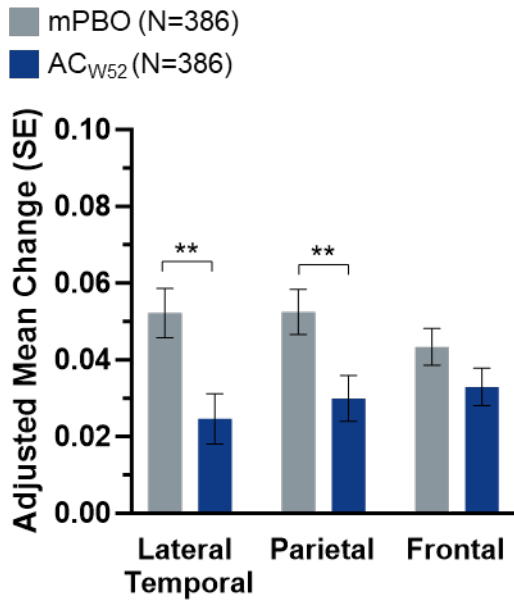


Figure S2: Change from baseline in tau PET at 76 weeks in donanemab-treated subgroups by amyloid clearance, weighted using inverse propensity scores calculated from baseline amyloid PET level and age.

Cerebellar crus used as reference region. The weighted mean (SD) baseline age in the AC_{W52} and NAC_{W52} subgroups was 72.8 (7.6) years and 72.5 (10.7) years, respectively. The weighted mean (SD) baseline amyloid PET level in the AC_{W52} and NAC_{W52} subgroups was 104.0 (45.1) CL and 103.9 (57.0) CL, respectively. Only subjects with a non-missing baseline value and at least one non-missing post-baseline value for the response variable were included in the analysis. Propensity score was derived using baseline amyloid PET level and age, with amyloid clearance status as dependent variable. P-values were derived from an ANCOVA model assessing the change from baseline difference by AC_{W52} vs NAC_{W52}, adjusting for baseline tau PET value and category. **p<0.01 and ***p<0.001 vs NAC_{W52}.

Abbreviations: AC_{W52}, amyloid <24.1 CL at week 52; AD, Alzheimer's disease; ANCOVA, analysis of covariance; CL, Centiloid; NAC_{W52}, amyloid ≥24.1 CL at week 52; PET, positron emission tomography; SE, standard error; SUVR, standardized uptake value ratio.

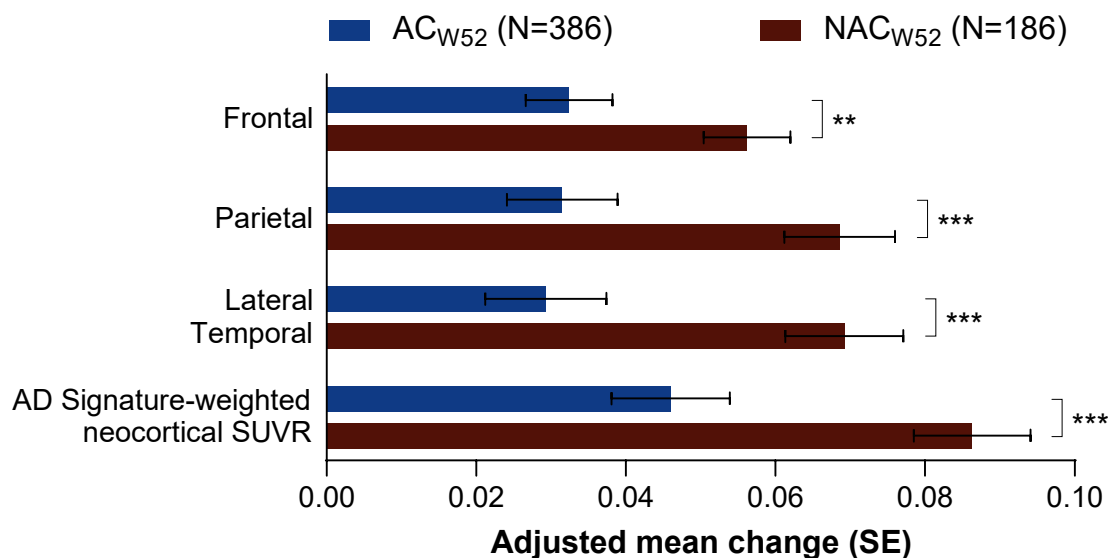


Table S1: Baseline characteristics of participants with an amyloid level <24.1 CL at 24 weeks or 52 weeks who received all scheduled donanemab doses (until that timepoint) and corresponding mPBO subgroup

	AC_{w24,52}	
	mPBO (N=311)	Donanemab (N=311)
Sex, n (%)		
Female	180 (57.9)	183 (58.8)
Male	131 (42.1)	128 (41.2)
Age, mean (SD), years	73.8 (6.0)	74.0 (6.1)
Weight, mean (SD), kg	70.7 (16.3)	70.4 (15.3)
Race, n (%) ^a		
Asian	27 (8.7)	22 (7.1)
Black or African American	9 (2.9)	4 (1.3)
White	275 (88.4)	282 (91.0)
American Indian or Alaska Native	0 (0.0)	2 (0.6)
Ethnicity, n (%) ^b		
Hispanic/Latino	13 (6.0)	11 (5.1)
Not Hispanic/Latino	205 (94.0)	206 (94.9)
APOE ε4 carrier, n (%)	182 (58.5)	186 (60.0)
APOE genotype, n (%)		
ε2/ε2	1 (0.3)	0 (0.0)
ε2/ε3	8 (2.6)	12 (3.9)
ε2/ε4	7 (2.3)	7 (2.3)
ε3/ε3	120 (38.6)	112 (36.1)
ε3/ε4	146 (46.9)	152 (49.0)
ε4/ε4	29 (9.3)	27 (8.7)
Acetylcholinesterase inhibitors/memantine use, n (%)	177 (56.9)	182 (58.5)
Clinical outcomes^c		
iADRS score, mean (SD)	105.2 (13.1)	104.6 (13.6)
CDR-SB score, mean (SD)	3.8 (2.0)	3.9 (2.1)
MMSE score ^d , mean (SD)	22.4 (3.9)	22.6 (3.8)
MMSE category, n (%) ^e		
Mild cognitive impairment (≥27)	59 (19.0)	60 (19.3)
Mild AD (20-26)	251 (81.0)	250 (80.4)
Moderate AD (<20)	0 (0)	1 (0.3)
CDR-G score, n (%)		
0	1 (0.3)	0 (0.0)
0.5	204 (65.6)	193 (62.7)
1	96 (30.9)	106 (34.4)
2	10 (3.2)	9 (2.9)
Biomarker measures, mean (SD)		
Amyloid plaque level, in Centiloids ^{e,f}	95.0 (31.8)	94.9 (31.9)
Tau SUVR ^{e,g}	1.3 (0.2)	1.3 (0.2)

Notes: Percentages were calculated using the number of participants with non-missing data as the denominator. Matched placebo-treated participants were selected using propensity score matching based on age, baseline amyloid plaque level, baseline tau SUVR, and number of APOE ε4 alleles.

^a Race data was collected as self-reported by participants within fixed categories.

^b Ethnicity reporting was limited to participants in the United States/Puerto Rico only.

^c Clinical outcome score ranges were as follows: CDR-G scores range from 0 (no dementia) to 3 (severe dementia); CDR-SB scores range from 0 to 18, with higher scores indicating greater clinical impairment;

iADRS scores range from 0 to 144, with lower scores indicating greater impairment; and MMSE scores range from 0 to 30, with lower scores indicating greater impairment.

^d Last non-missing MMSE score prior to or at the start of study treatment.

^e Based on screening data.

^f Assessed with 18F-florbetapir or 18F-florbetaben PET.

^g Assessed with 18F-flortaucipir PET. Global tau uptake was measured using a composite neocortical SUVR with white matter signal reference (1).

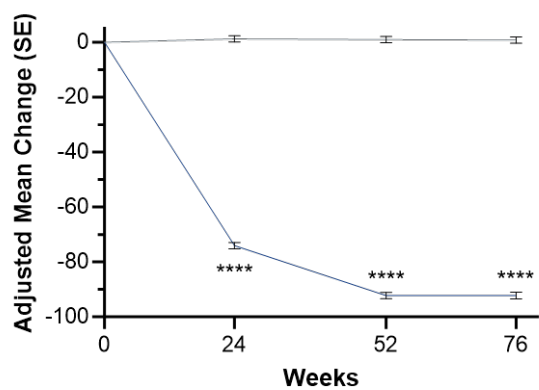
Abbreviations: AC_{W24,52}, amyloid <24.1 CL at week 24 or 52 and received all scheduled doses until treatment completion criteria were met; AD, Alzheimer's disease; APOE, apolipoprotein E; CDR-G, Clinical Dementia Rating Scale–Global Score; CDR-SB, Clinical Dementia Rating Scale–Sum of Boxes; iADRS, integrated Alzheimer's Disease Rating Scale; MMSE, Mini–Mental State Examination; mPBO, matched placebo; N, number of randomized participants; PET, positron emission tomography; SUVR, standardized uptake value ratio.

Figure S3. Efficacy in participants with an amyloid level <24.1 CL at 24 weeks or 52 weeks who received all scheduled donanemab doses (until that timepoint) compared with corresponding mPBO subgroup

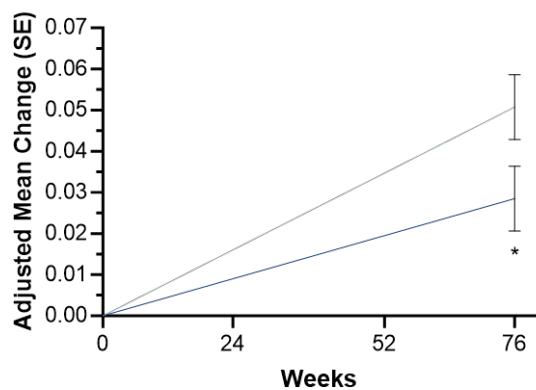
Time courses showing the trajectories of amyloid PET (CL) (A), lateral temporal tau PET SUVR (B), Log₁₀ plasma P-tau217 (C), Log₁₀ plasma GFAP (D), CDR-SB (E), and iADRS (F) in the AC_{W24,52} subgroup compared with mPBO. Data are shown as the least-squares mean (SE) change from baseline. Tau PET SUVR used the cerebellar crus as the reference region, and p-values were derived from an ANCOVA model. Least-squares mean, SE, and p-values for all other analyses were derived using a mixed model for repeated measures. CDR-SB scores range from 0 to 18, with higher scores indicating greater clinical impairment; iADRS scores range from 0 to 144, with lower scores indicating greater impairment. *p<0.05, **p<0.01, ***p<0.001, and ****p<0.0001 vs mPBO.

Abbreviations: AC_{W24,52}, amyloid <24.1 CL at week 24 or 52 and received all scheduled doses until treatment completion criteria were met; CDR-SB, Clinical Dementia Rating Scale—Sum of Boxes; CL, Centiloids; GFAP, glial fibrillary acidic protein; iADRS, integrated Alzheimer's Disease Rating Scale; mPBO, matched placebo; PET, positron emission tomography; P-tau217, phosphorylated tau 217; SE, standard error; SUVR, standardized uptake value ratio.

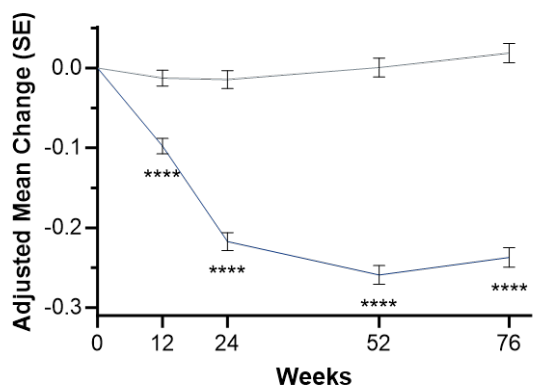
A) Amyloid PET



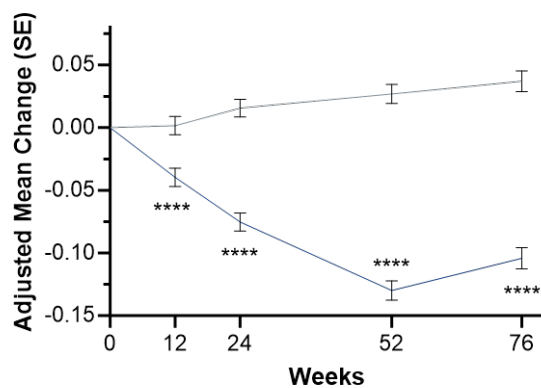
B) Tau PET



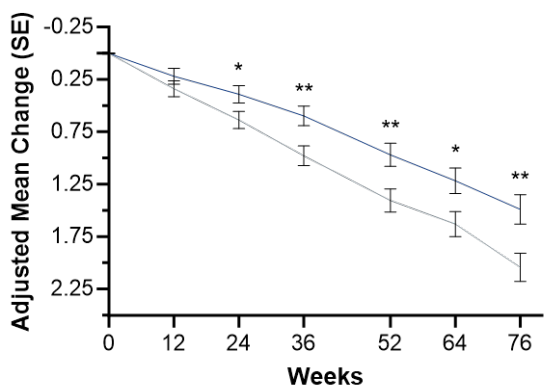
C) Plasma P-tau217



D) Plasma GFAP



E) CDR-SB



F) iADRS

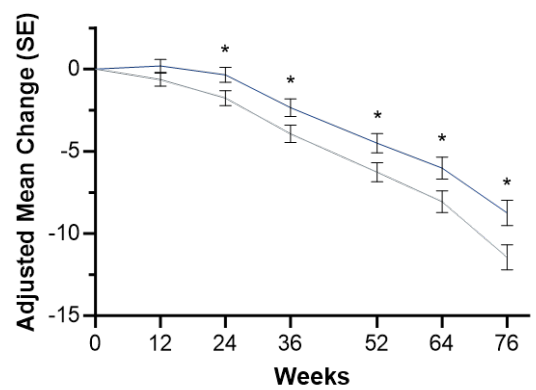


Table S2: Adverse events of special interest in donanemab-treated participants

Category, n (%)	Placebo-controlled study		Open-label addendum	
	AC_{w52} (N=443)	NAC_{w52} (N=227)	AC_{w52} (N=684)	NAC_{w52} (N=197)
Participants with ≥ 1 serious adverse event	65 (14.7)	32 (14.1)	123 (18.0)	38 (19.3)
ARIA-E	1 (0.2)	2 (0.9)	1 (0.1)	2 (1.0)
ARIA-H	0 (0.0)	1 (0.4)	2 (0.3)	1 (0.5)
ARIA-E based on MRI or TEAE cluster	95 (21.4)	61 (26.9)	112 (16.4)	61 (31.0)
ARIA-H based on MRI or TEAE cluster	124 (28.0)	95 (41.9)	163 (23.8)	77 (39.1)

Note: Events included occurred up to either the first visit date of the long-term extension phase –1 day or the end of the treatment period in the double-blinded phase +57 days, whichever occurred first.

Abbreviations: AC_{w52}, amyloid <24.1CL at week 52; ARIA-E, amyloid-related imaging abnormality with edema/effusion; ARIA-H, amyloid-related imaging abnormality with microhaemorrhages and haemosiderin deposits; MRI, magnetic resonance imaging; NAC_{w52}, amyloid ≥24.1CL at week 52; TEAE, treatment-emergent adverse event.

1. Devous MD, Sr., Joshi AD, Navitsky M, Southeikal S, Pontecorvo MJ, Shen H, et al. Test-Retest Reproducibility for the Tau PET Imaging Agent Flortaucipir F 18. J Nucl Med. 2018;59(6):937-43.