Supplemental Online Content

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Supplement 3. eMethods and eResults

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

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eTable 1. Trial Site Characteristics

Trial Site Characteristics	
Geography, No. of sites (% enrolled)	
United States	192 (69.3)
Outside of the United States[a]	85 (30.7)
Specialties of treating clinicians, No. of sites/total No. of sites (% enrolled)[b]	
Geriatrics	4/192 (2.1)
Psychiatry	36/192 (18.8)
Neurology	87/192 (45.3)
Primary care	40/192 (20.8)
Other	25/192 (13.0)
Clinical settings of administration, No. of sites/total No. of sites (% enrolled)[b]	
Community-based clinic/Non-academic	174/192 (90.6)
Academic/Research	18/192 (9.4)

[a] Countries outside of the United States included: Australia, Canada, Czech Republic, Great Britain, Japan, the Netherlands, and Poland.
[b] In the United States only.

eTable 2. Guidance in Managing ARIA-E and ARIA-H in TRAILBLAZER-ALZ 2

Finding	Symptoms	MRI Severity	Guidance
ARIA-E[a]	Asymptomatic	Mild to moderate (Severity rating 1-3)	- Hold IP if severity 3 and occurs within first 3 doses of the double-blind or long-term extension period, otherwise may continue IP - Monitor with unscheduled MRIs monthly until resolution
		Moderate+ to severe (Severity rating 4-5)	- Hold IP - Monitor with unscheduled MRIs monthly - Upon resolution of ARIA-E on imaging, consider re-initiating IP - If resolution is not observed, permanently discontinue IP, but continue other study activities
	Symptomatic	Any severity	- Hold IP - Monitor with unscheduled MRIs monthly - Upon resolution of ARIA-E on imaging and resolution of clinical symptoms, consider re-initiating IP - If resolution of ARIA-E or resolution of symptoms are not observed, permanently discontinue IP, but continue other study activities - If ARIA-E symptoms are clearly related to an SAE, then permanently discontinue IP, but continue other study activities
ARIA-H[b] Microhemorrhage, superficial siderosis	Asymptomatic	≤10 new microhemorrhages from baseline and/or ≤2 superficial sideroses	- Hold IP if >4 new microhemorrhages or 1 new superficial siderosis within first 3 doses of the double-blind or long-term extension period, otherwise may continue IP - Monitor with unscheduled MRIs monthly
		>10 new microhemorrhages from baseline and/or >2 superficial sideroses	- Hold IP - Monitor with unscheduled MRIs monthly - Upon stabilization of ARIA-H on imaging, consider re-initiating IP (stabilization defined as no new/increased superficial siderosis and not more than 1 new microhemorrhage on subsequent MRI)
	Symptomatic	Any severity	- Hold IP - Monitor with unscheduled MRIs monthly - If resolution of symptoms is not observed, permanently discontinue IP, but continue other study activities - If ARIA-H symptoms are clearly related to an SAE, then permanently discontinue IP, but continue other study activities
ARIA-H Macrohemorrhage	Asymptomatic or symptomatic	Any severity	- Permanently discontinue IP, but continue other study activities - Monitor with unscheduled MRIs monthly

Abbreviations: ARIA-E, amyloid-related imaging abnormalities-edema/effusions; ARIA-H, amyloid-related imaging abnormality-microhaemorrhages and haemosiderin deposits; IP, investigational product; MRI, magnetic resonance imaging; SAE, serious adverse event.

[a] ARIA-E Severity Rating Scale in central MRI reports.

1. Mild: Mild fluid-attenuated inversion recovery (FLAIR) hyperintensity confined to sulcus and/or cortex/subcortex white matter (with or without gyral swelling and sulcal effacement), which affects an area of less than 5 cm in a single greatest dimension. Only a single region of involvement detected.
2. Mild+: Mild FLAIR hyperintensity confined to sulcus and/or cortex/subcortex white matter (with or without gyral swelling and sulcal effacement), which affects an area of less than 5 cm in a single greatest dimension. More than one region of involvement detected.
3. Moderate: Moderate involvement (area of FLAIR hyperintensity measuring 5 to 10 cm in single greatest dimensions). Only a single region of involvement detected.
4. Moderate+: Moderate involvement (area of FLAIR hyperintensity measuring 5 to 10 cm in single greatest dimensions) in more than one site of involvement, each measuring less than 10 cm in a single greatest dimension.
5. Severe: Severe involvement (area of FLAIR hyperintensity measuring greater than 10 cm in single greatest dimension [white matter and/or sulcal involvement with associated gyral swelling and sulcal effacement]). One or more separate/independent sites of involvement may be noted.

[b] ARIA-H radiographic stabilization is defined as no new/increased superficial siderosis and not more than 1 new microhemorrhage on subsequent MRI

eTable 3. Summary of Screening Failure

Screen Failure Details	No. (%)
Screened	8420 (100.0)
Screen failure	6504 (78.9)
Reasons for screen failure[a,b]	
Flortaucipir	1631 (25.1%)
Florbetapir	1601 (24.6%)
MMSE	1510 (23.2%)
Withdrawal by Subject	465 (7.1%)
P-tau181[c]	295 (4.5%)
Reliability	259 (4.0%)
MRI	234 (3.6%)
Current Serious or Unstable Illness	76 (1.2%)
Clinically Important Abnormality	75 (1.2%)
Significant Neurological Disease	40 (0.6%)
Study Partner	38 (0.6%)
Physician Decision	32 (0.5%)
History of Cancer	29 (0.4%)
Age	28 (0.4%)
Poor Venous Access	23 (0.4%)
ALT/AST/TBL/ALP	21 (0.3%)
Withdrawal Due to Caregiver Circumstances	21 (0.3%)

Abbreviations: AD, Alzheimer's Disease; ALT, Alanine aminotransaminase; AST, aspartate aminotransferase; TBL, total bilirubin level; ALP, alkaline phosphatase; MMSE, Mini–Mental State Examination; MRI, magnetic resonance imaging; PET, positron emission tomography; P-tau181, phosphorylated tau 181; SUVR, standardized uptake value ratio

[a] Reasons for screen failure percentages are based on number of subjects screen failed rather than total number screened.

[b] Reasons for screen failure with a minimum of 20 participants are listed.

[c] Plasma P-tau181 exclusion applied to individuals who screened under the original protocol and amendment (a), but this criterion was removed in amendment (b) Feb 2021

eTable 4. Baseline Demographics and Clinical Characteristics in the High-tau Population

Population	High-tau	
Variable	**Donanemab (n=271)**	**Placebo (n=281)**
Sex, No. (%)		
Female	167 (61.6)	181 (64.4)
Male	104 (38.4)	100 (35.6)
Age, mean (SD), in years	70.1 (6.2)	70.5 (6.3)
Race, No. (%)[a]		
Asian	9 (3.3)	9 (3.2)
Black or African American	2 (0.7)	4 (1.4)
White	258 (95.6)	267 (95.0)
American Indian or Alaska Native	1 (0.4)	0
Multiple	0	1 (0.4)
Missing	1 (0.4)	0
Race, US only, No./total No. (%) [a]		
Asian	4/203 (2.0)	1/214 (0.5)
Black or African American	1/203 (0.5)	3/214 (1.4)
White	197/203 (97.0)	209/214 (97.7)
American Indian or Alaska Native	1/203 (0.5)	0
Multiple	0	1/214 (0.5)
Ethnicity in the US study population, No. (%)[b]		
Hispanic/Latino	11 (5.4)	10 (4.7)
Not Hispanic/Latino	192 (94.6)	203 (95.3)
Education of ≥13 years, No. (%)	198 (73.3)	215 (76.5)
APOE carrier, No. (%)	176 (65.4)	193 (68.9)
E2/E2	0	0
E2/E3	8 (3.0)	6 (2.1)
E2/E4	5 (1.9)	6 (2.1)
E3/E3	85 (31.6)	81 (28.9)
E3/E4	118 (43.9)	141 (50.4)
E4/E4	53 (19.7)	46 (16.4)
Acetylcholinesterase inhibitors/memantine use, No. (%)	188 (69.4)	197 (70.1)
Clinical measures, mean (SD)[c]		
iADRS score	100.6 (14.7)	99.4 (13.8)
CDR-SB score	4.4 (2.0)	4.4 (2.0)
ADAS-Cog$_{13}$ score	31.4 (9.1)	32.3 (9.2)
ADCS-ADL score	65.6 (8.9)	65.3 (8.0)
ADCS-iADL score	47.1 (8.0)	46.7 (7.6)
MMSE score[d]	21.1 (3.9)	20.8 (3.9)
MMSE category, No. (%)[e]		
Mild cognitive impairment (≥27)	31 (11.4)	21 (7.5)
Mild AD (20-26)	240 (88.6)	260 (92.5)
Moderate AD (<20)	0	0
CDR-G score, No. (%)		
0	0	1 (0.4)
0.5	132 (50.0)	144 (52.0)
1	126 (47.7)	123 (44.4)
2	6 (2.3)	9 (3.2)

Biomarker measures, mean (SD)		
Amyloid plaque level, mean (SD), in Centiloids[f]	106.0 (33.8)	103.1 (33.1)
AD signature weighted neocortical flortaucipir SUVR, mean (SD)[1,d,g]	1.68 (0.17)	1.70 (0.20)
Plasma P-tau217, mean (SD), in pg/mL[h]	9.4 (20.2)	9.9 (21.4)

Numbers of participants with non-missing data were used as denominators to calculate percentages.
Abbreviations: AchEI, acetylcholinesterase inhibitors; AD, Alzheimer's Disease; ADAS-Cog_{13}, 13-item cognitive subscale of the Alzheimer's Disease Assessment Scale; ADCS-ADL, Alzheimer's Disease Cooperative Study – Activities of Daily Living; ADCS-iADL, Alzheimer's Disease Cooperative Study – Instrumental Activities of Daily Living; APOE, Apolipoprotein E; CDR-G, Clinical Dementia Rating Global Score; CDR-SB, Clinical Dementia Rating Scale–Sum of Boxes; iADRS, Integrated Alzheimer's Disease Rating Scale; MMSE, Mini–Mental State Examination; N, number of randomized participants; PET, positron emission tomography; P-tau217, phosphorylated tau 217; SUVR, standardized uptake value ratio

[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; percentages were calculated using the number of participants with non-missing data as the denominator.

[c] Clinical outcome ranges were as follows: ADAS-Cog_{13} scores range from 0 to 85, with higher scores indicating greater overall cognition deficit; ADCS-ADL scores range from 0 to 78, with lower scores indicating greater level of impairment; ADCS-iADL scores range from 0 to 59, with lower scores indicating greater impairment in daily function; 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 level of 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]

[h] Plasma P-tau217 denotes plasma-measured phosphorylated tau at threonine 217, a blood biomarker specific to AD and associated with both amyloid and tau pathology.[2]

eTable 5. Clinical Outcomes from Baseline to 76 weeks in the High-tau Population

Outcome[a]	Group	Donanemab			Placebo					
		Baseline, mean (SD)	76 w, mean (SD)	LSM Change (95% CI)	Baseline, mean (SD)	76 w, mean (SD)	LSM Change (95% CI)	LSM difference versus placebo (95% CI)	P-value versus placebo	% slowing[b] (95% CI)
iADRS	**High-tau**	[n=242]	[n=165]	-	[n=263]	[n=208]	-	-	-	-
	NCS2	101.51 (13.83)	86.01 (23.06)	-19.51 (-21.74, -17.27)	99.27 (13.81)	83.13 (21.12)	-20.76 (-22.84, -18.69)	1.26 (-1.77, 4.28)	0.415	6.0 (-8.50, 20.59)
	MMRM[c]	101.51 (13.83)	86.01 (23.06)	-18.29 (-20.61, -15.97)	99.27 (13.82)	83.13 (21.12)	-19.23 (-21.43, -17.03)	0.94 (-2.17, 4.04)	0.554	4.9 (-11.24, 20.99)
CDR-SB	**High-tau**	[n=248]	[n=174]	-	[n=268]	[n=212]	-	-	-	-
	NCS2	4.36 (1.91)	6.75 (3.42)	2.77 (2.42, 3.12)	4.43 (2.04)	7.24 (3.37)	3.33 (3.00, 3.65)	-0.56 (-1.03, -0.09)	0.021	16.8 (2.53, 31.04)
	MMRM[c]	4.36 (1.91)	6.75 (3.42)	2.64 (2.27, 3.01)	4.43 (2.04)	7.24 (3.37)	3.34 (2.98, 3.69)	-0.69 (-1.19, -0.20)	0.006	20.8 (5.88, 35.77)
ADCS-iADL	**High-tau**	[n=245]	[n=171]	-	[n=263]	[n=209]	-	-	-	-
	NCS2	47.42 (7.76)	40.62 (11.97)	-8.24 (-9.54, -6.94)	46.71 (7.56)	39.48 (11.24)	-9.25 (-10.45, -8.04)	1.01 (-0.76, 2.78)	0.264	10.9 (-8.25, 30.06)
	MMRM[c]	47.42 (7.76)	40.62 (11.97)	-7.83 (-9.20, -6.47)	46.71 (7.56)	39.48 (11.24)	-8.82 (-10.13, -7.52)	0.99 (-0.82, 2.81)	0.283	11.2 (-9.32, 31.80)
ADAS-Cog$_{13}$	**High-tau**	[n=247]	[n=176]	-	[n=270]	[n=216]	-	-	-	-
	NCS2	31.02 (9.01)	39.95 (13.53)	10.57 (9.40, 11.73)	32.42 (9.28)	41.63 (12.18)	11.08 (9.99, 12.17)	-0.51 (-2.11, 1.09)	0.531	4.6 (-9.79, 18.99)
	MMRM[c]	31.02 (9.01)	39.95 (13.53)	10.08 (8.77, 11.39)	32.42 (9.28)	41.63 (12.18)	10.49 (9.25, 11.73)	-0.40 (-2.12, 1.31)	0.643	3.9 (-12.46, 20.18)
MMSE	**High-tau**	[n=247]	[n=171]	-	[n=267]	[n=214]	-	-	-	-
	NCS2	21.21 (3.96)	17.47 (5.66)	-4.39 (-4.91, -3.86)	20.73 (3.86)	16.50 (5.49)	-4.74 (-5.23, -4.25)	0.35 (-0.37, 1.07)	0.334	7.5 (-7.67, 22.58)

	MMRM[c]	21.21 (3.96)	17.47 (5.66)	-4.37 (-4.99, -3.75)	20.73 (3.86)	16.50 (5.49)	-4.70 (-5.29, -4.11)	0.33 (-0.48, 1.15)	0.421	7.1 (-10.18, 24.36)

Abbreviations: ADAS-Cog_{13}, 13-item cognitive subscale of the Alzheimer's Disease Assessment Scale; ADCS-iADL, Alzheimer's Disease Cooperative Study – instrumental Activities of Daily Living; CDR-SB, Clinical Dementia Rating Scale–Sum of Boxes; CI, confidence interval; iADRS, Integrated Alzheimer's Disease Rating Scale; LSM, least squares mean; MMRM, mixed model for repeated measures; MMSE, Mini–Mental State Examination; NCS2, Natural Cubic Spline with 2 degrees of freedom; SD, standard deviation.

[a] Clinical outcomes were scored as follows: ADAS-Cog13 scores range from 0 to 85, with higher scores indicating greater overall cognition deficit; ADCS-iADL scores range from 0 to 59, with lower scores indicating greater impairment in daily function; 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 level of impairment.

[b] The % slowing is obtained by dividing the treatment difference between donanemab and placebo at 76 weeks by the placebo decline at 76 weeks, and then multiplying by 100.

[c] For MMRM analyses, 95% CIs for LS mean changes were calculated with the normal approximation method.

eTable 6. Time-Based Analyses

Population	Low/medium-tau		Combined[e]	
	Donanemab	Placebo	Donanemab	Placebo
Delayed disease progression at 76w as measured by iADRS[a,b]				
Months saved vs placebo (95% CI)	4.36 (1.87, 6.85)	-	2.47 (1.12, 3.82)	-
Percent time savings (95% CI)	24.87 (10.68, 39.07)	-	14.08 (6.36, 21.79)	-
P value vs placebo	<0.001	-	<0.001	-
Delayed disease progression at 76w as measured by CDR-SB[a,c]				
Months saved vs placebo (95% CI)	7.53 (5.69, 9.36)	-	5.44 (3.90, 6.98)	-
Percent time savings (95% CI)	42.9 (32.44, 53.37)	-	31.0 (22.21, 39.79)	-
P value vs placebo	<0.001	-	<0.001	-
No progression at 52w as measured by CDR-SB[a,d]				
Estimated percent of no progression (95% CI)	47% (42, 51)	29% (25, 33)	36% (33, 40)	23% (20, 26)
P value vs placebo	<0.00001	-	<0.001	-

Abbreviations: CDR-SB, Clinical Dementia Rating Scale–Sum of Boxes; iADRS, Integrated Alzheimer's Disease Rating Scale

[a] iADRS scores range from 0 to 144, with lower scores indicating greater impairment, and CDR-SB scores range from 0 to 18, with higher scores indicating greater clinical impairment.

[b] The model did not assume proportional time slowing. Results from the prespecified test of proportional time slowing assumption at 76 weeks was 2.61 months saved (95% CI: 1.17, 4.05; *P*=0.002), but the proportional time slowing assumption was not met for the iADRS (*P* = 0.001 from a likelihood ratio test).

[c] The model assumed proportional time slowing.

[d] No progression was defined as a CDR-SB score change from baseline of less than or equal to 0.

[e] Not prespecified as gated in the statistical analysis plan (Supplement 2).

eTable 7. Summary of adverse events leading to treatment discontinuation in ≥0.5% participants in the donanemab group during the placebo-controlled period.

AEs Leading to Treatment Discontinuation, n (%)	Donanemab (N = 853)	Placebo (N = 874)
Participants with treatment discontinuation due to AEs	112 (13.1)	38 (4.3)
IRR	31 (3.6)	0
ARIA-E	21 (2.5)	3 (0.3)
ARIA-H	7 (0.8)	2 (0.2)
Hypersensitivity	4 (0.5)	0

Abbreviations: AE, adverse event; ARIA-E, amyloid-related imaging abnormality–edema/effusions; ARIA-H = amyloid-related imaging abnormality–microhemorrhages and hemosiderin deposits (including brain microhemorrhage and superficial siderosis); IRR = infusion-related reaction; N, number of participants

eTable 8. Radiographic and clinical severity of ARIA by APOE4 carrier status

	Donanemab, N (%)				Placebo, N (%)			
	APOE4 noncarrier (N=255)	APOE4 carrier (N=595)	APOE4 Heterozygote (N=452)	APOE4 Homozygote (N=143)	APOE4 noncarrier (N=250)	APOE4 Carrier (N=620)	APOE4 Heterozygote (N=474)	APOE4 Homozygote (N=146)
ARIA-E[a]	40 (15.7)	161 (27.1)	103 (22.8)	58 (40.6))	2 (0.8)	14 (2.3)	9 (1.9)	5 (3.4)
Mild	13 (5.1)	44 (7.4)	30 (6.6)	14 (9.8)	2 (0.8)	11 (1.8)	8 (1.7)	3 (2.1)
Mild+	14 (5.5)	61 (10.3)	37 (8.2)	24 (16.8)	0	2 (0.3)	1 (0.2)	1 (0.7)
Moderate	7 (2.7)	9 (1.5)	7 (1.5)	2 (1.4)	0	0	0	0
Moderate +	5 (2.0)	34 (5.7)	20 (4.4)	14 (9.8)	0	1 (0.2)	0	1 (0.7)
Severe	1 (0.4)	13 (2.2)	9 (2.0)	4 (2.8)	0	0	0	0
Serious ARIA-E	1	12	8	4	0	0	0	0
ARIA-H[b]	48 (18.8)	218 (36.6)	146 (32.3)	72 (50.3)	28 (11.2)	87 (14.0)	57 (12.0)	30 (20.5)
Mild	33 (12.9)	92 (15.5)	68 (15.0)	24 (16.8)	23 (9.2)	69 (11.1)	47 (9.9)	22 (15.1)
Moderate	4 (1.6)	48 (8.1)	35 (7.7)	13 (9.1)	3 (1.2)	14 (2.3)	9 (1.9)	5 (3.4)
Severe	11 (4.3)	78 (13.1)	43 (9.5)	35 (24.5)	2 (0.8)	4 (0.6)	1 (0.2)	3 (2.1)
Serious ARIA-H	1	3	1	2	0	0	0	0
ARIA-H microhemorrhage	39 (15.3)	180 (30.3)	121 (26.8)	59 (41.3)	27 (10.8)	76 (12.3)	50 (10.5)	26 (17.8)
ARIA-H superficial siderosis	19 (7.5)	115 (19.3)	75 (16.6)	40 (28.0)	3 (1.2)	22 (3.5)	12 (2.5)	10 (6.8)
Macrohemorrhage	0	3	3	0	0	1	1	0
Serious macrohemorrhage	0	1	1	0	0	0	0	0

Abbreviations: AE, adverse event; ARIA-E, amyloid-related imaging abnormality–edema/effusions; ARIA-H = amyloid-related imaging abnormality–microhemorrhages and hemosiderin deposits (including brain microhemorrhage and superficial siderosis); IRR = infusion-related reaction; N, number of participants

ARIA-E, ARIA-H, and macrohemorrage are by MRI. SAEs are by AE reporting

[a] ARIA-E severity described in detail in eTable 2

[b] ARIA-H severity classification is based on highest severity classification of either ARIA-H microhemorrhage or superficial siderosis. ARIA-H microhemorrhage severity definitions: mild = ≤4 new incident microhemorrhages, moderate = 5-9 new incident microhemorrhages, severe = ≥10 new incident microhemorrhages. ARIA-H superficial siderosis severity definitions: mild = 1 new or increased focal area of superficial siderosis, moderate = 2 new or increased focal area of superficial siderosis, severe = >2 new or increased focal area of superficial siderosis

eTable 9. Patient Death Vignettes

During the placebo-controlled portion of the study, three participants had SAEs of ARIA and subsequently died. These participants were 72-75 years old at study enrollment. Two participants were male, and one was female; all were white. Two participants were APOE ε4 heterozygous carriers and one was a non-carrier. Screening amyloid PET ranged from 74-132 centiloids. All had low/medium baseline tau on screening PET scan. None were prescribed antithrombotic medications. None of these participants had an MRI prior to their second dose, since they had passed that timepoint prior to protocol implementation of the Week 4 MRI monitoring. None had autopsy performed.

Participant 1	Had a fatal SAE of ARIA-E. The participant had no baseline ARIA-H. Ten days after the 3rd dose of donanemab 700 mg, the participant was hospitalized for confusion, agitation, and speech difficulties. No MRIs were performed during hospitalization. CT angiogram on admission reported potential subacute right-sided stroke and multifocal areas of vasogenic edema in the right cerebral hemisphere. A CT 6 days later reported possible new foci of subarachnoid hemorrhage; extensive vasogenic edema throughout the right cerebral hemisphere, and probably some within the left occipital lobe remained stable. The participant received dexamethasone for 12 days and died 14 days after SAE onset.
Participant 2	Had a fatal SAE of ARIA-H. The participant had superficial siderosis (50 mm) on screening MRI. After 2 doses of donanemab 700 mg, infusions were held for mild symptomatic ARIA-E associated with headache. On MRI 25 days later, ARIA-E (2+ mild[a]), 1 new microhemorrhage, 3 new areas of superficial siderosis, and increased size of the pre-existing superficial siderosis were observed. The following day, the participant was hospitalized for unstable gait, hemiplegia, and aphasia, with severe cerebral hemorrhage and hemorrhagic stroke with mass effect. The participant died 3 days after SAE onset.
Participant 3	Had a fatal SAE of death. The participant had no baseline ARIA-H, and a prior occurrence of severe asymptomatic ARIA-E and ARIA-H after 3 doses of donanemab 700 mg. Upon resolution of ARIA-E, donanemab was resumed, with 4 additional doses of donanemab 700 mg then 3 doses of 1400 mg. The participant developed confusion, balance disorder, nausea, and vomiting and was hospitalized for SAEs of ARIA-E and ARIA-H four weeks after the last dose. Dexamethasone was administered. The participant died 20 days after SAE onset.

[a] See eTable 2 for definition of the 5 point radiographic severity scale

eTable 10. Summary of Adverse Events in the Low/medium-tau and High-tau population

Population	Low/medium-tau		High-tau	
Participants[a]	**Donanemab (n=584)**	**Placebo (n=593)**	**Donanemab (n=268)**	**Placebo (n=280)**
Overview of adverse events (AEs), No. (%)				
Death[b]	12 (2.1)[c]	8 (1.3)	4 (1.5)	2 (0.7)
Participants with ≥1 serious AE[d]	97 (16.6)	97 (16.4)	51 (19.0)	41 (14.6)
Treatment discontinuations due to AEs	82 (14.0)	27 (4.6)	30 (11.2)	11 (3.9)
Study discontinuations due to AEs	50 (8.6)	24 (4.0)	19 (7.1)	8 (2.9)
Participants with ≥1 treatment-emergent AE[e]	522 (89.4)	498 (84.0)	237 (88.4)	219 (78.2)
Treatment-emergent AEs ≥5% Incidence, No. (%)[f]				
Amyloid-related imaging abnormalities-edema/effusions (ARIA-E)	138 (23.6)	13 (2.2)	67 (25.0)	4 (1.4)
Amyloid-related imaging abnormality microhemorrhages and hemosiderin deposits (ARIA-H)	109 (18.7)	41 (6.9)	59 (22.0)	24 (8.6)
COVID-19	94 (16.1)	106 (17.9)	42 (15.7)	48 (17.1)
Headache	77 (13.2)	57 (9.6)	42 (15.7)	29 (10.4)
Fall	83 (14.2)	78 (13.2)	31 (11.6)	32 (11.4)
Infusion-related reaction	53 (9.1)	2 (0.3)	21 (7.8)	2 (0.7)
Superficial siderosis of central nervous system	40 (6.8)	9 (1.5)	18 (6.7)	1 (0.4)
Dizziness	42 (7.2)	41 (6.9)	11 (4.1)	7 (2.5)
Arthralgia	39 (6.7)	28 (4.7)	10 (3.7)	14 (5.0)
Urinary tract infection	30 (5.1)	37 (6.2)	15 (5.6)	21 (7.5)
Diarrhea	28 (4.8)	34 (5.7)	15 (5.6)	16 (5.7)
Fatigue	31 (5.3)	33 (5.6)	11 (4.1)	12 (4.3)
Overview of ARIA				
Any ARIA (ARIA-E or ARIA-H), No. (%)[g]	211 (36.1)	90 (15.2)	103 (38.4)	40 (14.3)
ARIA-E, No. (%)	138 (23.6)	13 (2.2)	67 (25.0)	5 (1.8)
Asymptomatic	102 (17.5)	12 (2.0)	51 (19.0)	5 (1.8)
Symptomatic	36 (6.2)	1 (0.2)[h]	16 (6.0)	0
ARIA-H, No. (%)	179 (30.7)	82 (13.8)	89 (33.2)	37 (13.2)
Microhemorrhage	146 (25.0)	75 (12.6)	83 (31.0)	34 (12.1)
Superficial siderosis	88 (15.1)	19 (3.2)	46 (17.2)	7 (2.5)
Intracerebral hemorrhage >1 cm	3 (0.5)	1 (0.2)	0	1 (0.4)

Abbreviations: AE, adverse event; ARIA, amyloid-related imaging abnormalities; ARIA-E, amyloid-related imaging abnormalities-edema/effusions; ARIA-H, amyloid-related imaging abnormality-microhemorrhages and hemosiderin deposits; COVID-19, COronaVIrus Disease of 2019; MRI, magnetic resonance imaging; TEAE, treatment-emergent adverse event.

[a] Participants may have been counted in more than one category; adverse events population is defined as all participants that received at least one infusion.

[b] Deaths are also included under serious AEs and discontinuations due to AEs.

[c] Includes one death that occurred after treatment completion and in the follow-up period.

[d] Definition of serious AE: results in death, is life-threatening, required inpatient hospitalization or prolongation of existing hospitalization, results in persistent disability/incapacity, or based on other medical/scientific judgment

[e] Definition of treatment-emergent adverse event: An untoward medical occurrence that emerges during a defined treatment period, having been absent pretreatment, or worsens relative to the pretreatment state, and does not necessarily have to have a causal relationship with this treatment.

[f] Adverse events included are identical to Table 3 for consistency (≥5 % in the donanemab or total combined population). The only adverse event ≥5% in the donanemab or total low/medium-tau population not listed here was hypertension (5.0% with donanemab, 4.6% with placebo). Adverse events that were ≥5% in the donanemab or total high-tau population not listed here were nausea (6.3% with donanemab, 2.5% with placebo), anxiety (6.0% with donanemab, 5.7% with placebo), and depression (5.6% with donanemab, 3.6% with placebo).

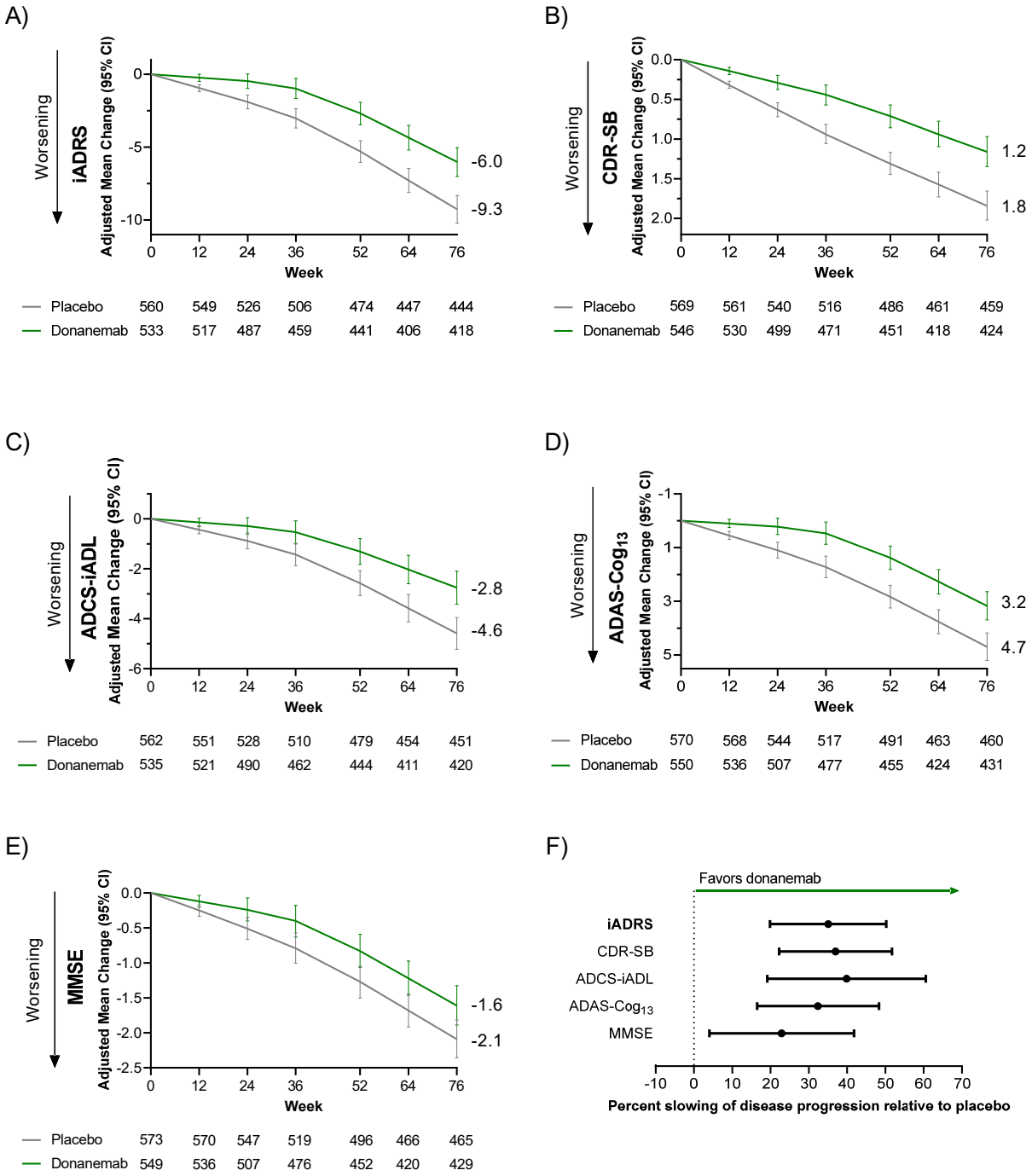
[g] Based on safety MRI or TEAE cluster (post-baseline).

[h] One placebo-treated participant had ARIA-E during the placebo-controlled period; however, the participant developed symptoms during the long-term extension period.

Figures

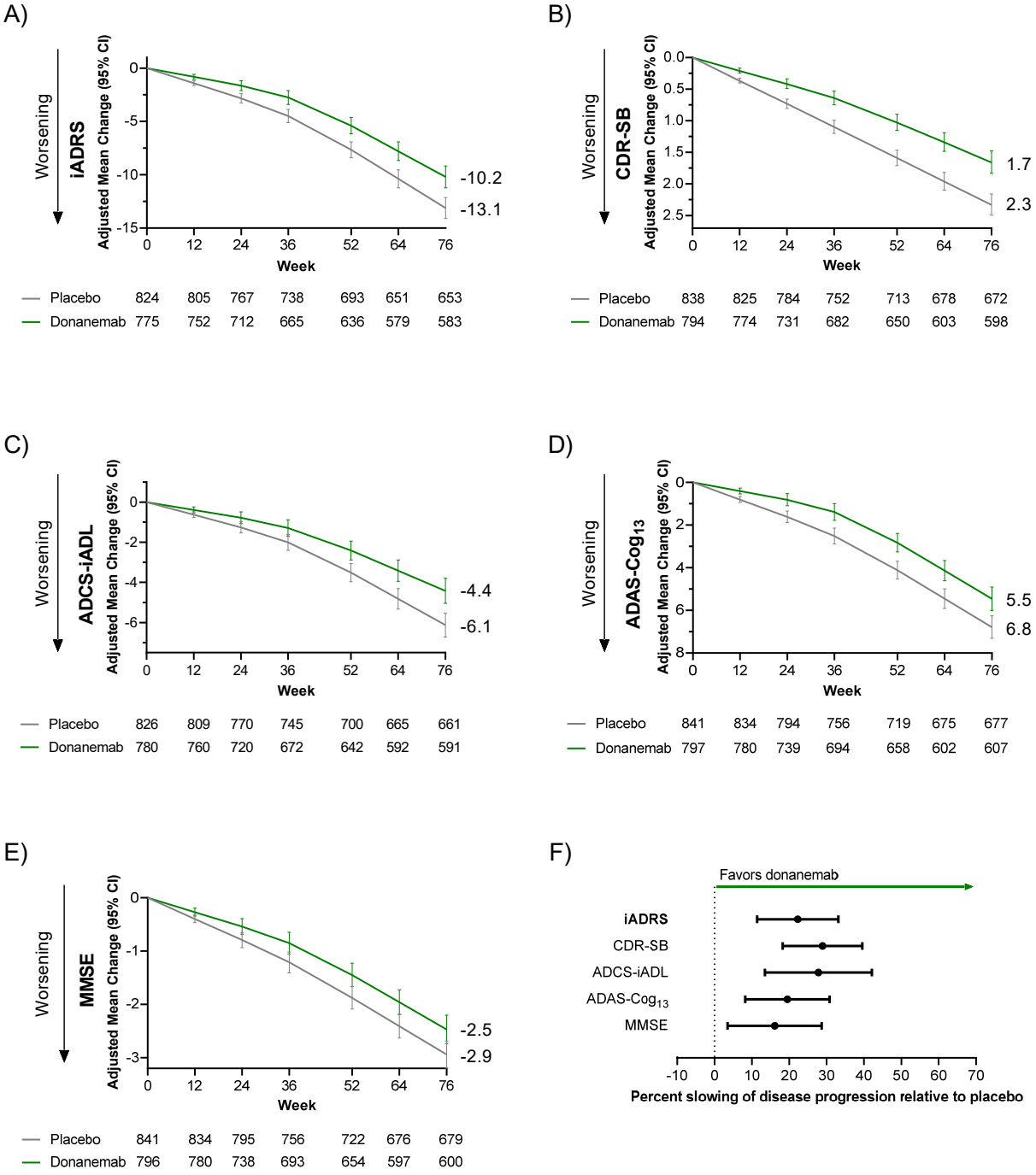
eFigure 1. NCS2 Analyses in the Low/medium-tau Population

Time course of change from baseline to 76 weeks in A) iADRS (p-value <0.0001 for all time points); 35.1% slowing (95% CI: 19.90, 50.23), B) CDR-SB (p-value <0.0001 for all time points); 37.0% slowing (95% CI: 22.26, 51.75), C) ADCS-iADL (p-value <0.05 at 12 and 24 weeks, <0.01 at 36 weeks, <0.001 at 52 and 64 weeks and <0.0001 at 76 weeks); 39.9% slowing (95% CI: 19.15, 60.58), D) ADAS-Cog_{13} (p-value <0.0001 for all time points) 32.4% slowing (95% CI: 16.55, 48.35), and E) MMSE (p-value <0.05 at 12, 24, 36, and 76 weeks, <0.01 at 52 and 64 weeks); 22.9% slowing (95% CI: 4.04, 41.84) in the low/medium-tau population. The percent slowing (with 95% CI) across all clinical scales in the low/medium-tau population at 76w are shown on each graph and collated in F). Data shown were analyzed using NCS2. Number of participants in each group, at each time point are shown below each graph. Abbreviations: ADAS-Cog_{13}, 13-item cognitive subscale of the Alzheimer's Disease Assessment Scale; ADCS-iADL, Alzheimer's Disease Cooperative Study – Instrumental Activities of Daily Living; CDR-SB, Clinical Dementia Rating Scale–Sum of Boxes; CI, confidence interval; iADRS, Integrated Alzheimer's Disease Rating Scale; MMSE, Mini–Mental State Examination.



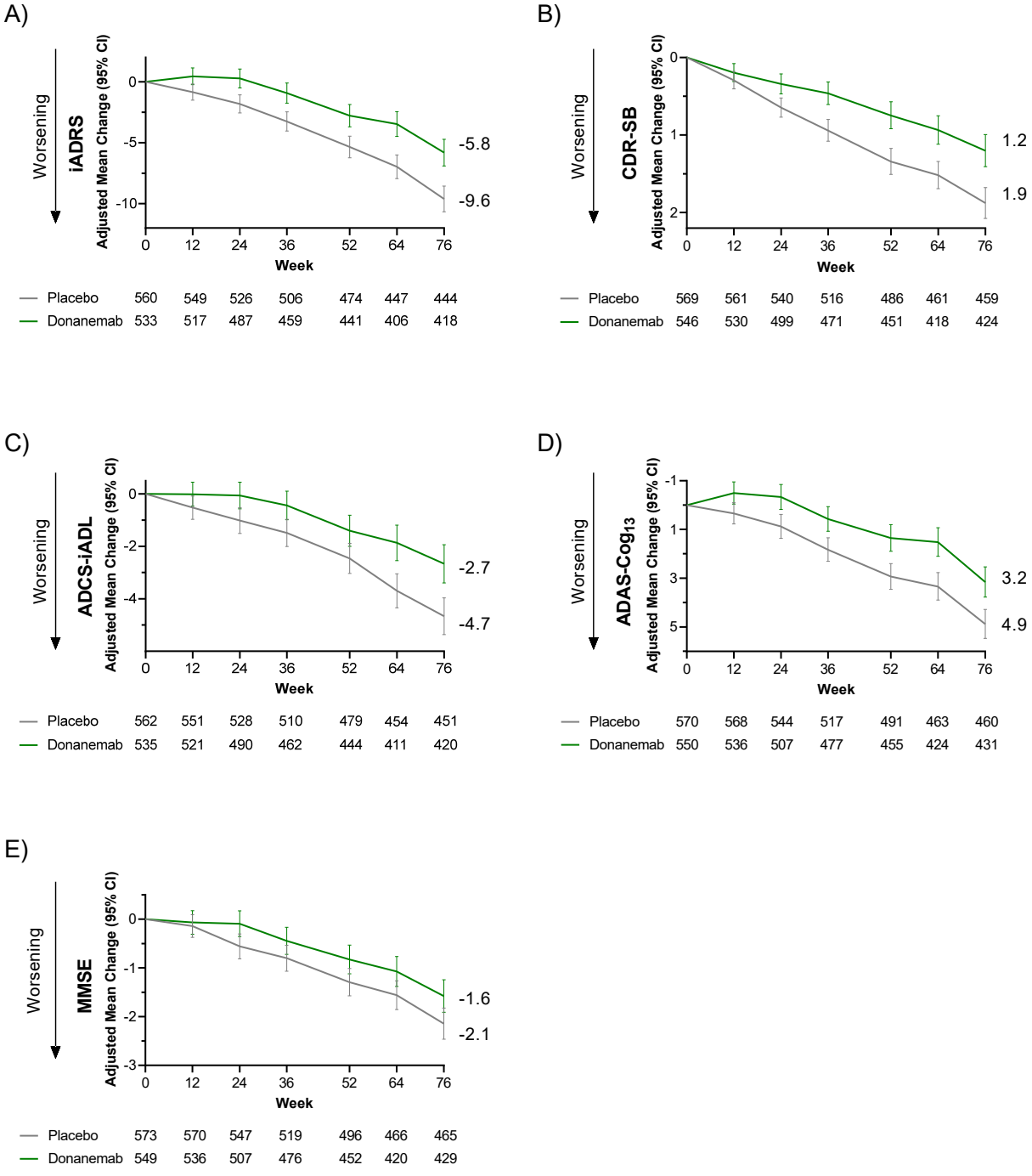
eFigure 2. NCS2 Analyses in the Combined Population

Time course of change from baseline to 76 weeks in A) iADRS (p-value <0.001 at 12, 24, and 36 weeks, and <0.0001 at 52, 64, and 76 weeks); 22.3% slowing (95%CI: 11.38, 33.15), B) CDR-SB (p-value <0.0001 for all time points); 28.9% slowing (95% CI: 18.26, 39.53), C) ADCS-iADL (p-value <0.05 at 12, 24, and 36 weeks, and <0.0001 at 52, 64, and 76 weeks); 27.8% slowing (95% CI: 13.48, 42.13), D) ADAS-Cog_{13} (p-value <0.0001 at 12, 24, 36, 52, and 64 weeks, and <0.001 at 76 weeks); 19.5% slowing (95% CI: 8.23, 30.83), and E) MMSE (p-value <0.05 at 12, 24, 36 and 76 weeks, and <0.01 at 52, and 64 weeks); 16.1% slowing (95% CI: 3.49, 28.67) in the combined population. The percent slowing (with 95% CI) across all clinical scales in the combined population at 76w are shown on each graph and collated in F). Data shown were analyzed using NCS2. Number of participants in each group, at each time point are shown below each graph. Please refer to Table 2 for p-values. . Abbreviations: ADAS-Cog_{13}, 13-item cognitive subscale of the Alzheimer's Disease Assessment Scale; ADCS-iADL, Alzheimer's Disease Cooperative Study – Instrumental Activities of Daily Living; CDR-SB, Clinical Dementia Rating Scale–Sum of Boxes; CI, confidence interval; iADRS, Integrated Alzheimer's Disease Rating Scale; MMSE, Mini–Mental State Examination.



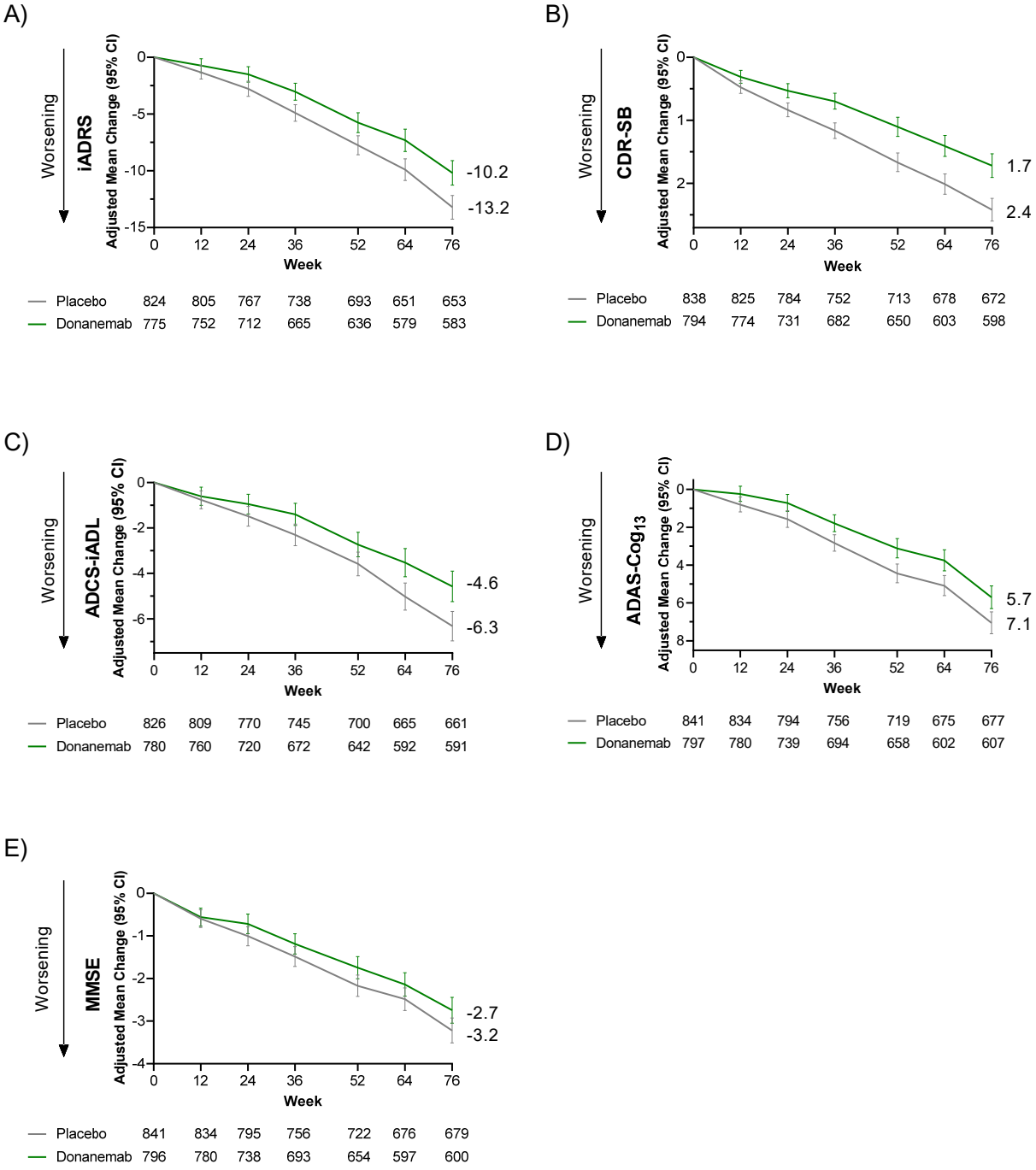
eFigure 3: MMRM Analyses in the Low/medium-tau Population

Time course of change from baseline to 76 weeks in A) iADRS (p-value <0.01 at 12 weeks, and <0.0001 for all subsequent timepoints); 39.6% slowing (95% CI: 23.93, 55.22), B) CDR-SB (p-value <0.001 at 24 weeks, <0.0001 for all subsequent timepoints); 36.0% slowing (95% CI: 20.76, 51.15), C) ADCS-iADL (p-value <0.01 at 24, 36, and 52 weeks, and <0.0001 at 64 and 76 weeks); 42.9% slowing (95% CI: 21.39, 64.44), D) ADAS-Cog_{13} (p-value <0.01 at 12 weeks, <0.001 at 24 weeks and <0.0001 for all subsequent timepoints); 35.3% slowing (95% CI: 18.27, 52.33), and E) MMSE (p-value <0.01 at 24 weeks, and <0.05 for all subsequent timepoints); 26.4% slowing (95% CI: 5.88, 47.01) in the low/medium -tau population. The percent slowing (with 95% CI) across all clinical scales at 76w are shown on each graph. Data shown were analyzed using MMRM. 95% CIs for LS mean changes were calculated with the normal approximation method. Number of participants in each group, at each time point are shown below each graph. Abbreviations: ADAS-Cog_{13}, 13-item cognitive subscale of the Alzheimer's Disease Assessment Scale; ADCS-iADL, Alzheimer's Disease Cooperative Study – Instrumental Activities of Daily Living; CDR-SB, Clinical Dementia Rating Scale–Sum of Boxes; CI, Confidence interval; iADRS, Integrated Alzheimer's Disease Rating Scale; MMSE, Mini–Mental State Examination.



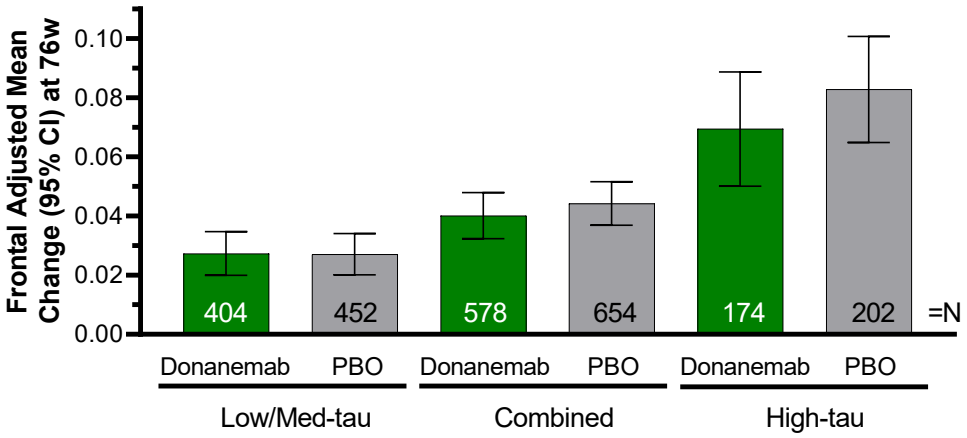
eFigure 4: MMRM Analyses in the Combined Population

Time course of change from baseline to 76 weeks in A) iADRS (p-value <0.01 at 24 weeks, <0.001 at 52 weeks, and <0.0001 at 36, 64 and 76 weeks); 22.9% slowing (95% CI: 11.96, 33.92), B) CDR-SB (p-value <0.01 at 12 weeks, and <0.0001 for all subsequent timepoints); 28.9% slowing (95% CI: 18.41, 39.44), C) ADCS-iADL (p-value <0.05 at 24 and 52 weeks, <0.01 at 36 weeks, and <0.001 at 64 and 76 weeks); 27.7% slowing (95% CI: 13.37, 42.00), D) ADAS-Cog_{13} (p-value <0.05 at 12 weeks, <0.01 at 24 weeks, <0.001 at 36, 64 and 76 weeks and <0.0001 at 52 weeks); 19.2% slowing (95% CI: 7.99, 30.38) and E) MMSE (p-value <0.05 at 24, 36, 52, and 76 weeks); 14.8% slowing (95% CI: 2.46, 27.06) in the combined population. The percent slowing (with 95% CI) across all clinical scales at 76w are shown on each graph. Data shown were analyzed using MMRM. 95% CIs for LS mean changes were calculated with the normal approximation method. Number of participants in each group, at each time point are shown below each graph. Abbreviations: ADAS-Cog_{13}, 13-item cognitive subscale of the Alzheimer's Disease Assessment Scale; ADCS-iADL, Alzheimer's Disease Cooperative Study – Instrumental Activities of Daily Living; CDR-SB, Clinical Dementia Rating Scale–Sum of Boxes; CI, Confidence interval; iADRS, Integrated Alzheimer's Disease Rating Scale; MMSE, Mini–Mental State Examination.



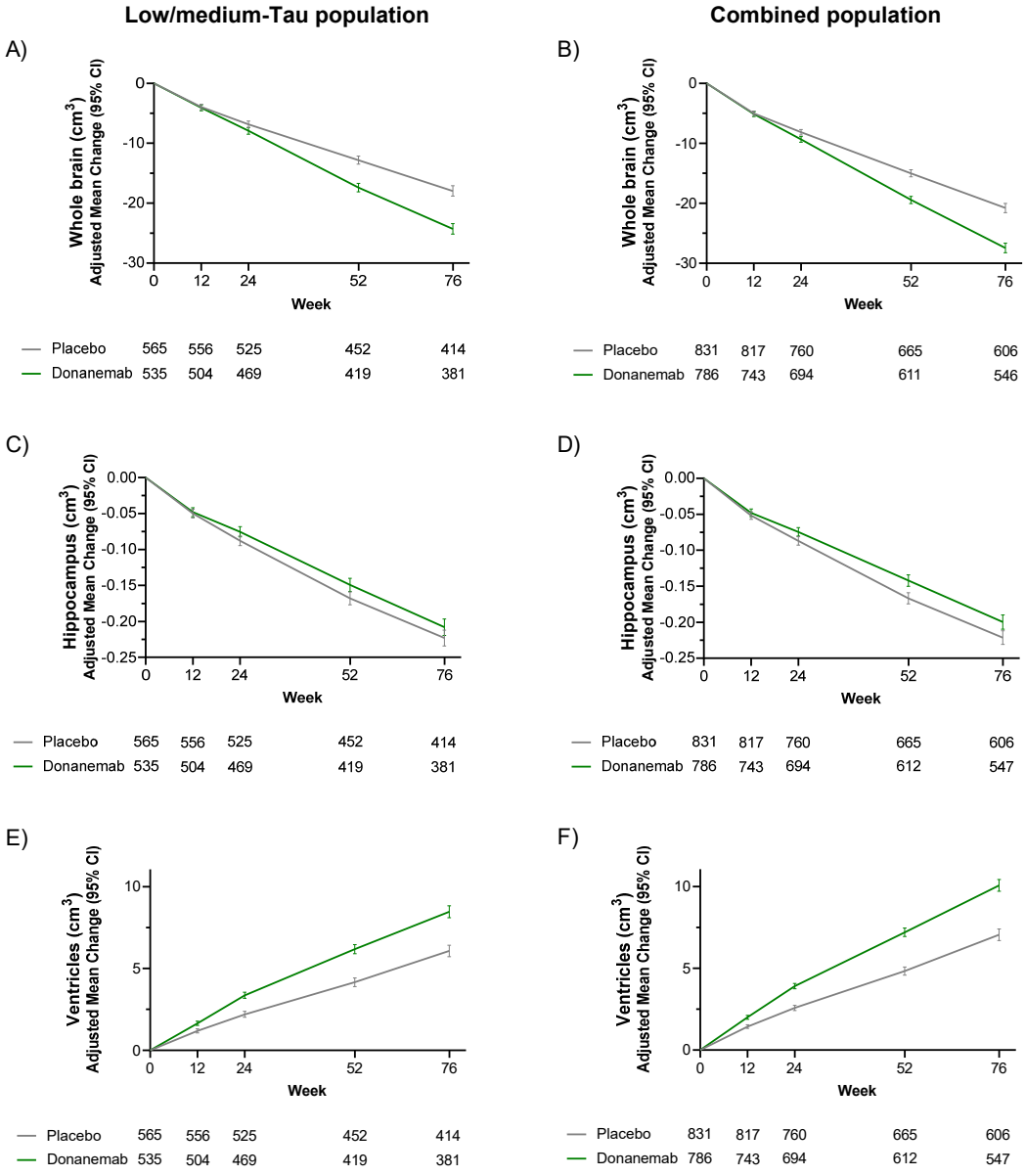
eFigure 5. Tau PET

Adjusted mean change in frontal tau SUVR at 76 weeks in the low/medium-tau, combined and high-tau populations. Tau PET data shown were analyzed using ANCOVA. 95% CIs for LS mean changes were calculated with the normal approximation method. Number of participants in each group are shown at the bottom of each bar. Abbreviations: ANCOVA, Analysis of Covariance; CI, confidence interval; PET, positron emission tomography; SUVR, standardized uptake value ratio



eFigure 6. Volumetric MRI in the Low/medium-tau and Combined Population

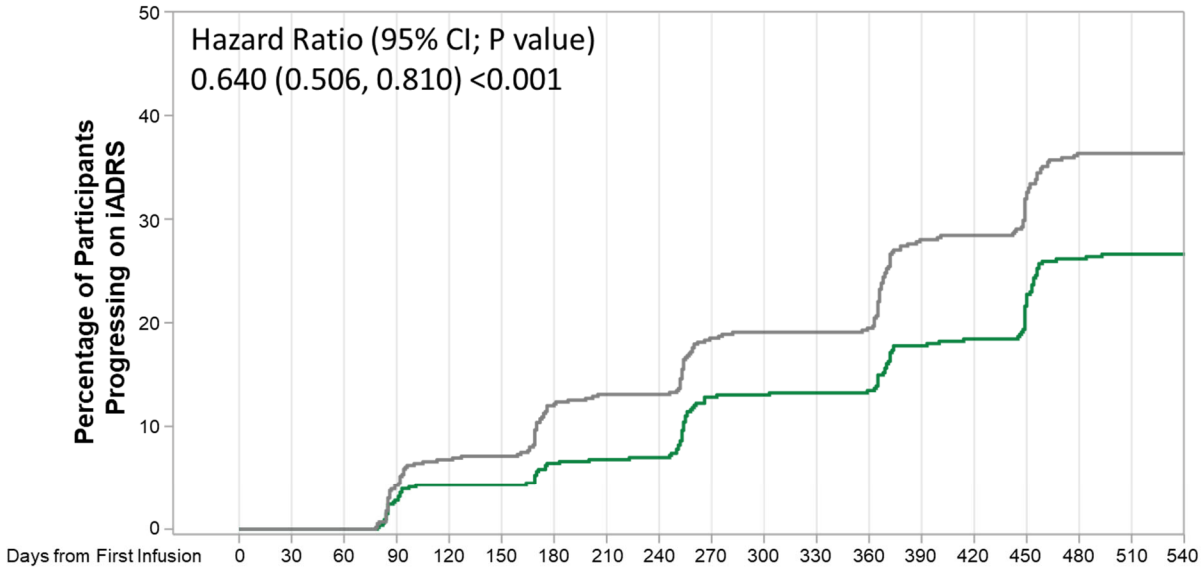
Time course of changes in volumetric MRI from baseline to 76 weeks in the low/medium-tau population by region in A) the whole brain (p-value <0.01 at 24 weeks, and <0.0001 at 52 and 76 weeks), C) the hippocampus (p- value <0.05 at 24 weeks, and <0.01 at 52 weeks) and E) the ventricles (p- value <0.0001 for all time points) and in the combined population by region in B) the whole brain (p- value <0.001 at 24 weeks, and <0.0001 at 52 and 76 weeks), D) the hippocampus (p- value <0.01 at 24 and 76 weeks, and <0.0001 at 52 weeks) and F) the ventricles (p- value <0.0001 for all time points). Data shown were analyzed using MMRM. Number of participants in each group, at each time point, are shown below each graph. Abbreviations: MMRM, mixed model for repeated measures; vMRI, volumetric magnetic resonance imaging



eFigure 7. iADRS and CDR-SB Hazard Plots

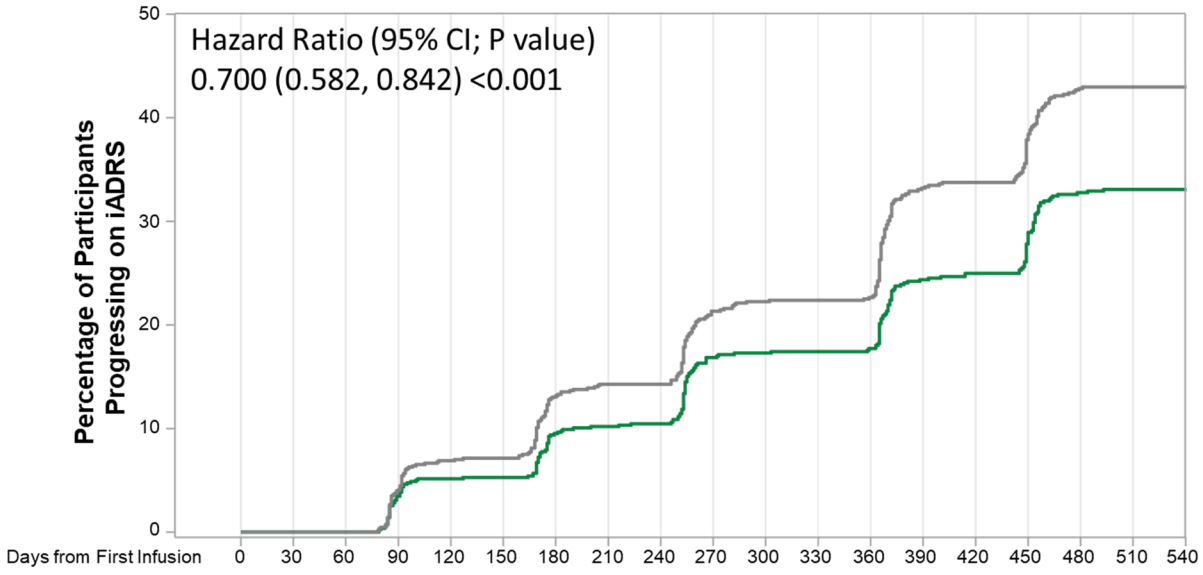
Cumulative hazard ratio indicating risk of progression assessed using the A) iADRS using the low/medium-tau population with substantial decline observed in 129 (24%) donanemab-treated participants and 190 (34%) placebo treated participants, B) iADRS using the combined population with substantial decline observed in 232 (29%) donanemab-treated participants and 329 (40%) placebo treated participants, C) CDR-SB using the low/medium-tau population with substantial decline observed in 130 (23%) donanemab-treated participants and 211 (37%) placebo treated participants, and D) CDR-SB using the combined population with substantial decline observed in 229 (28%) donanemab-treated participants and 348 (41%) placebo treated participants. The percentage (SE, n at risk) is shown in the table. Number of participants in each group, at each time point, are shown below each graph. CDR-SB, Clinical Dementia Rating Scale–Sum of Boxes; CL, Centiloids; CI, confidence interval; iADRS, Integrated Alzheimer's Disease Rating Scale; SE, standard error.

A)



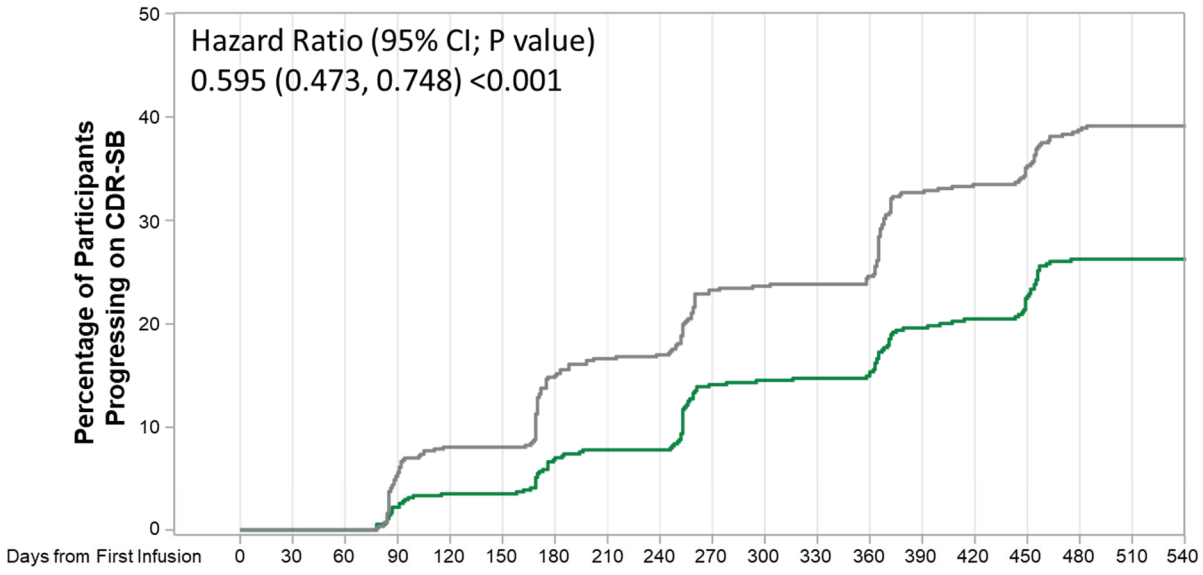
				Time, % (SE) n at risk					
Treatment	N	Event	60 days	120 days	180 days	240 days	360 days	480 days
Placebo	565	190	0.0 (0.00) 562	6.8 (1.06) 522	12.2 (1.38) 484	13.1 (1.43) 467	19.5 (1.69) 410	36.3 (2.12) 305
Donanemab	542	129	0.0 (0.00) 539	4.3 (0.88) 506	6.4 (1.06) 484	7.0 (1.11) 467	13.5 (1.51) 403	26.2 (2.02) 322

B)



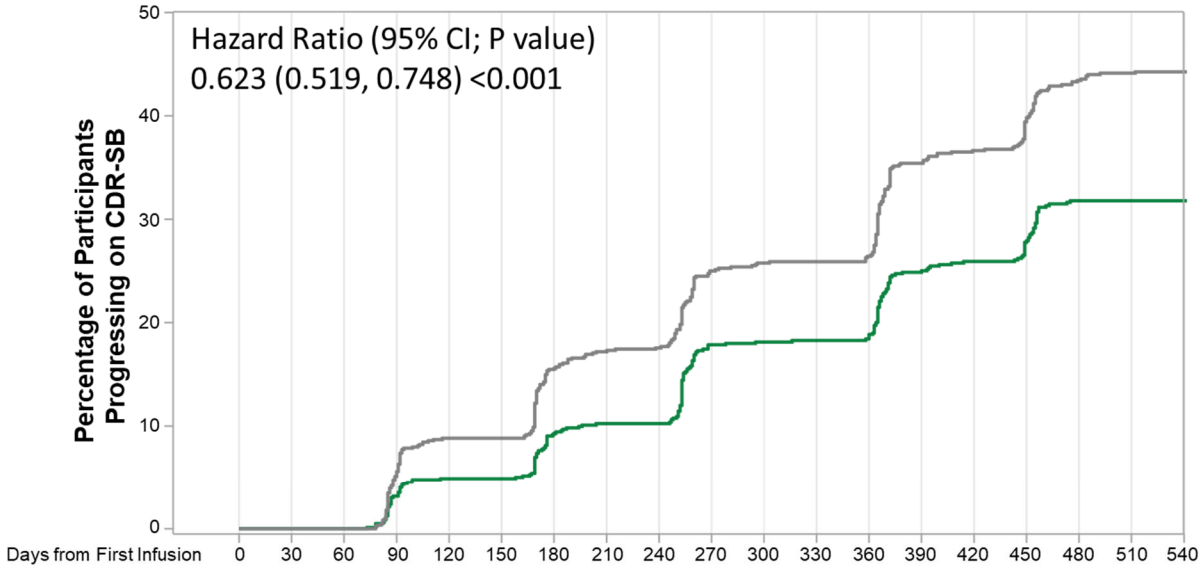
			Time, % (SE) n at risk					
Treatment	N	Event	60 days	120 days	180 days	240 days	360 days	480 days
Placebo	831	329	0.0 (0.00) 827	6.9 (0.88) 766	13.2 (1.18) 702	14.3 (1.22) 673	22.6 (1.48) 576	42.8 (1.81) 403
Donanemab	788	232	0.0 (0.00) 783	5.1 (0.79) 731	9.5 (1.06) 675	10.5 (1.11) 650	17.7 (1.40) 549	32.8 (1.80) 416

C)



			Time, % (SE) n at risk					
Treatment	N	Event	60 days	120 days	180 days	240 days	360 days	480 days
Placebo	573	211	0.0 (0.00) 570	8.1 (1.14) 522	15.0 (1.50) 475	17.0 (1.58) 453	24.6 (1.83) 393	38.7 (2.11) 302
Donanemab	555	130	0.0 (0.00) 552	3.5 (0.78) 523	7.0 (1.10) 492	7.8 (1.16) 471	15.4 (1.58) 403	26.3 (2.00) 327

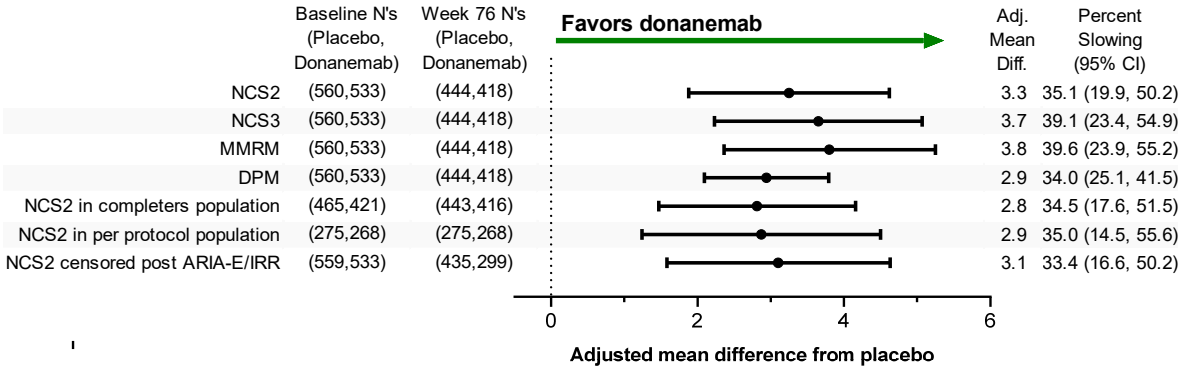
D)



			Time, % (SE) n at risk					
Treatment	N	Event	60 days	120 days	180 days	240 days	360 days	480 days
Placebo	844	348	0.0 (0.00) 840	8.8 (0.98) 762	15.6 (1.26) 693	17.6 (1.32) 658	26.4 (1.55) 559	43.4 (1.78) 406
Donanemab	805	229	0.0 (0.00) 801	4.9 (0.77) 750	9.3 (1.04) 693	10.2 (1.08) 666	18.9 (1.42) 559	31.8 (1.75) 435

eFigure 8. Sensitivity Analyses

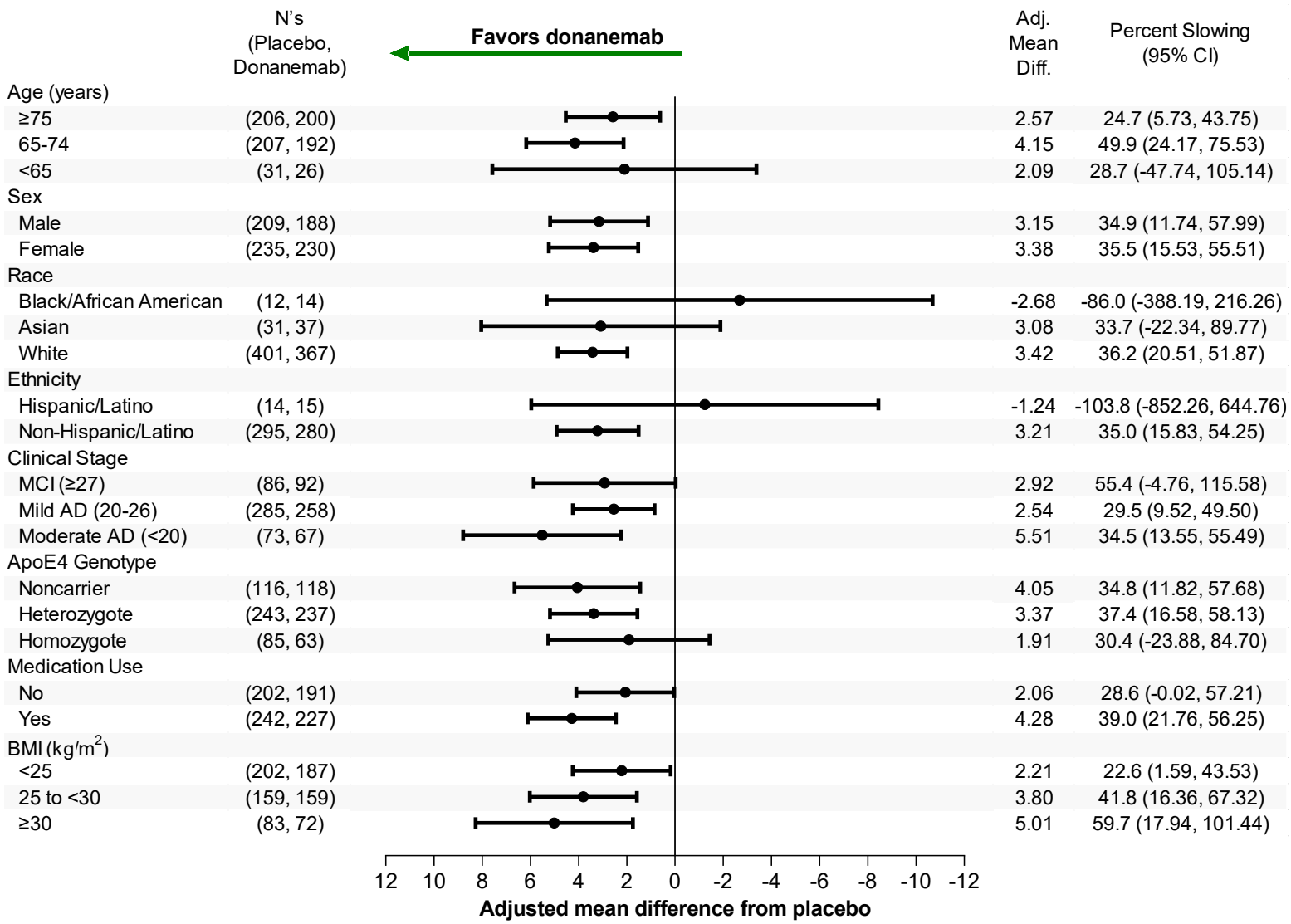
Sensitivity analyses of the treatment difference and percent slowing on the iADRS at 76 weeks in the donanemab group as compared with the placebo group in the low/medium -tau population. Results from the NCS analysis is provided for comparison. The efficacy evaluable population (all randomized participants with a baseline and at least one post-baseline efficacy scale) was assessed using the NCS3, MMRM, and DPM methods. In addition, the NCS2 was used to assess the completers (all randomized participants who have completed the placebo-controlled, double-blinded phase) and per protocol population (all participants in the efficacy evaluable set who also had an iADRS score for each scheduled visit and no protocol violations), as well as the efficacy evaluable population after censoring for ARIA-E and IRR. Bars show the 95% confidence intervals (except for DPM which shows credible intervals over the entire 18-month intervention period). The confidence intervals were not adjusted for multiple comparisons, and no definite conclusions can be drawn. Abbreviations: ARIA-E, amyloid-related imaging abnormalities-edema/effusion; CI, confidence interval; iADRS, Integrated Alzheimer's Disease Rating Scale; DPM, Disease Progression Model; IRR, infusion-related reactions; MMRM, mixed model repeated measures; MMSE, Mini–Mental State Examination; N, number of participants; NCS2, Natural Cubic Spline model with 2 degrees of freedom; NCS3, Natural Cubic Spline model with 3 degrees of freedom



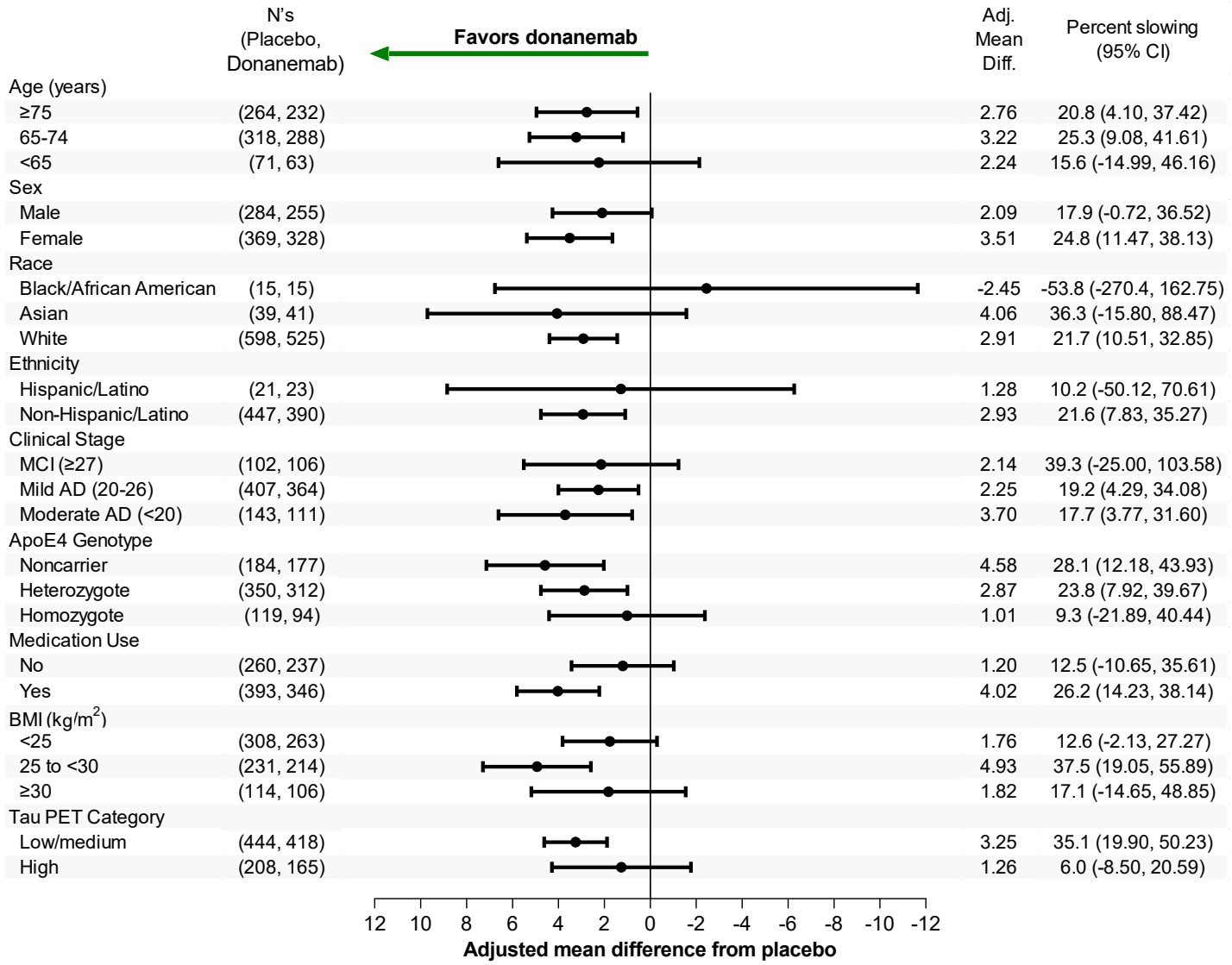
eFigure 9. Forest Plots of Baseline Characteristic Subgroups

Subgroup analyses of the adjusted mean difference at 76 weeks in the donanemab group as compared with the placebo group for A) the iADRS (low/medium-tau population), B) the iADRS (combined population), C) the CDR-SB (low/medium-tau population), D) the CDR-SB (combined population). The model includes the same baseline covariates as specified for the NCS primary efficacy analysis, with additional fixed terms of subgroup by treatment, subgroup by basis expansion, and subgroup by basis expansion by treatment interactions. Tau PET category data generated independently from each other. Bars show the 95% CI; values are included for those that extend past the limits of the axis. Abbreviations: Adj. mean Diff., Adjusted mean difference, AD, Alzheimer's Disease; APOE, apolipoprotein E; BMI, body mass index; CDR-SB, Clinical Dementia Rating Scale–Sum of Boxes; CI, Confidence interval; iADRS, Integrated Alzheimer’s Disease Rating Scale; MCI, mild cognitive impairment; N, number of participants; PET, positron emission tomography.

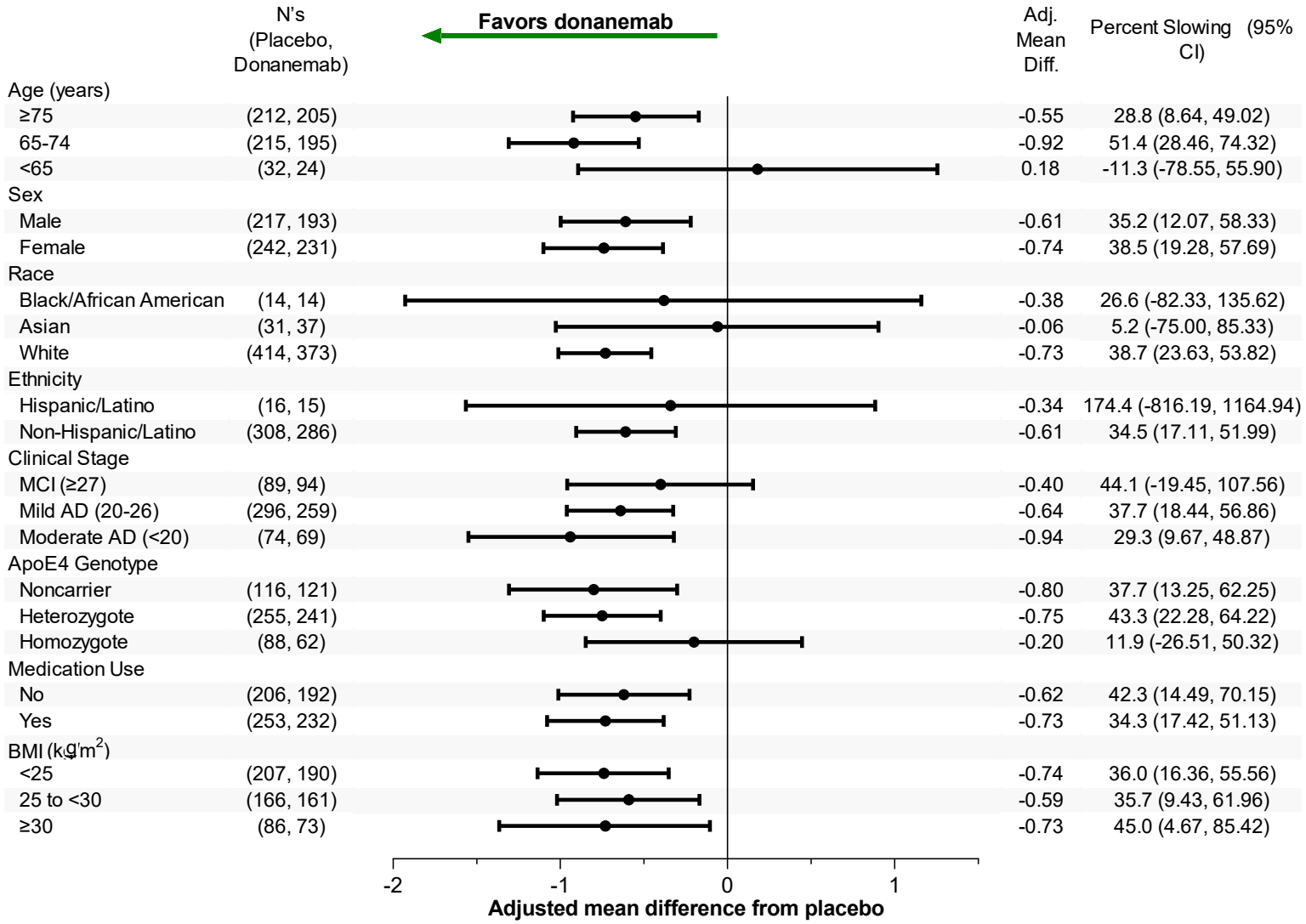
A) iADRS: Low/medium-tau Population



B) iADRS: Combined Population

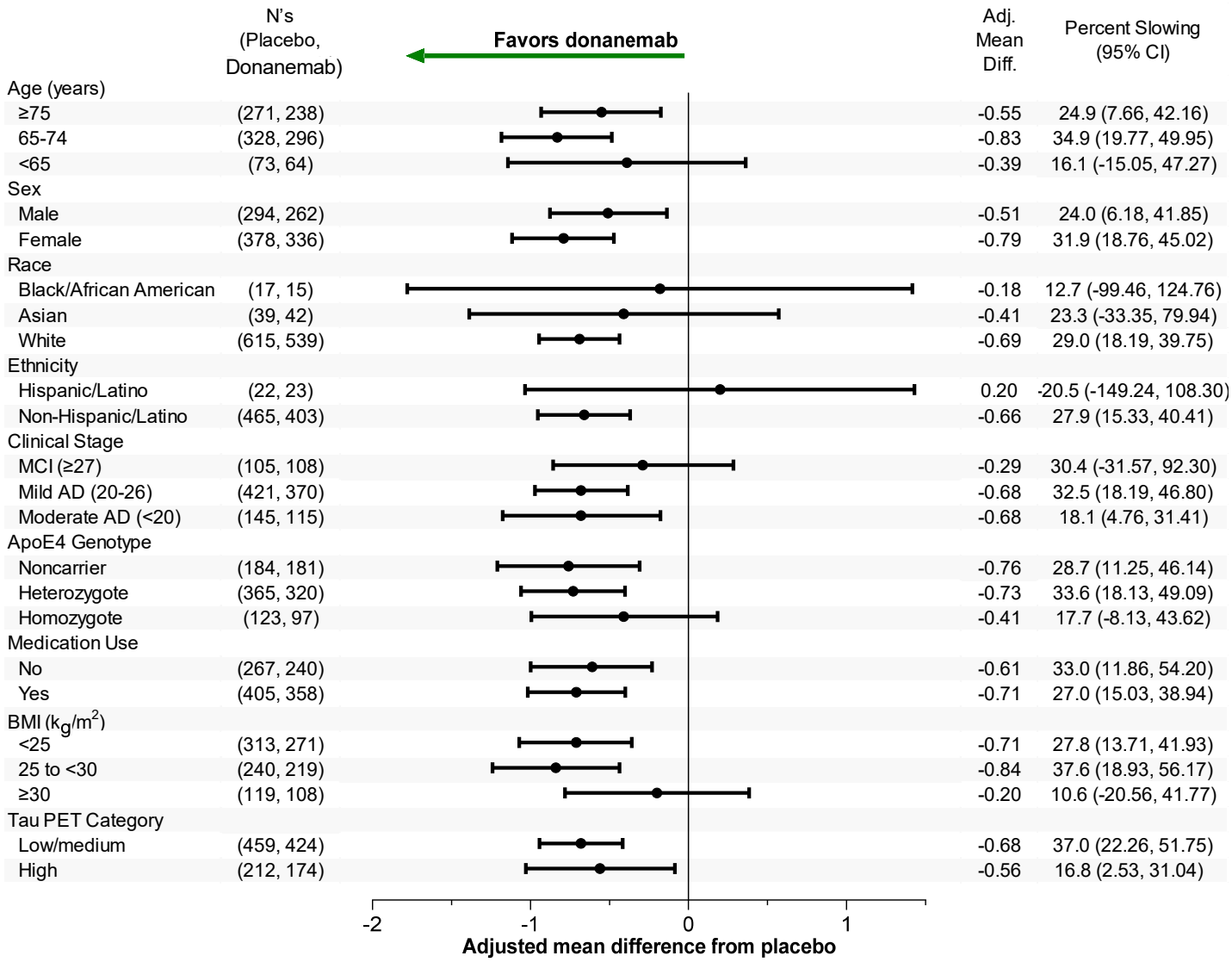


C) CDR-SB: Low/medium-tau Population



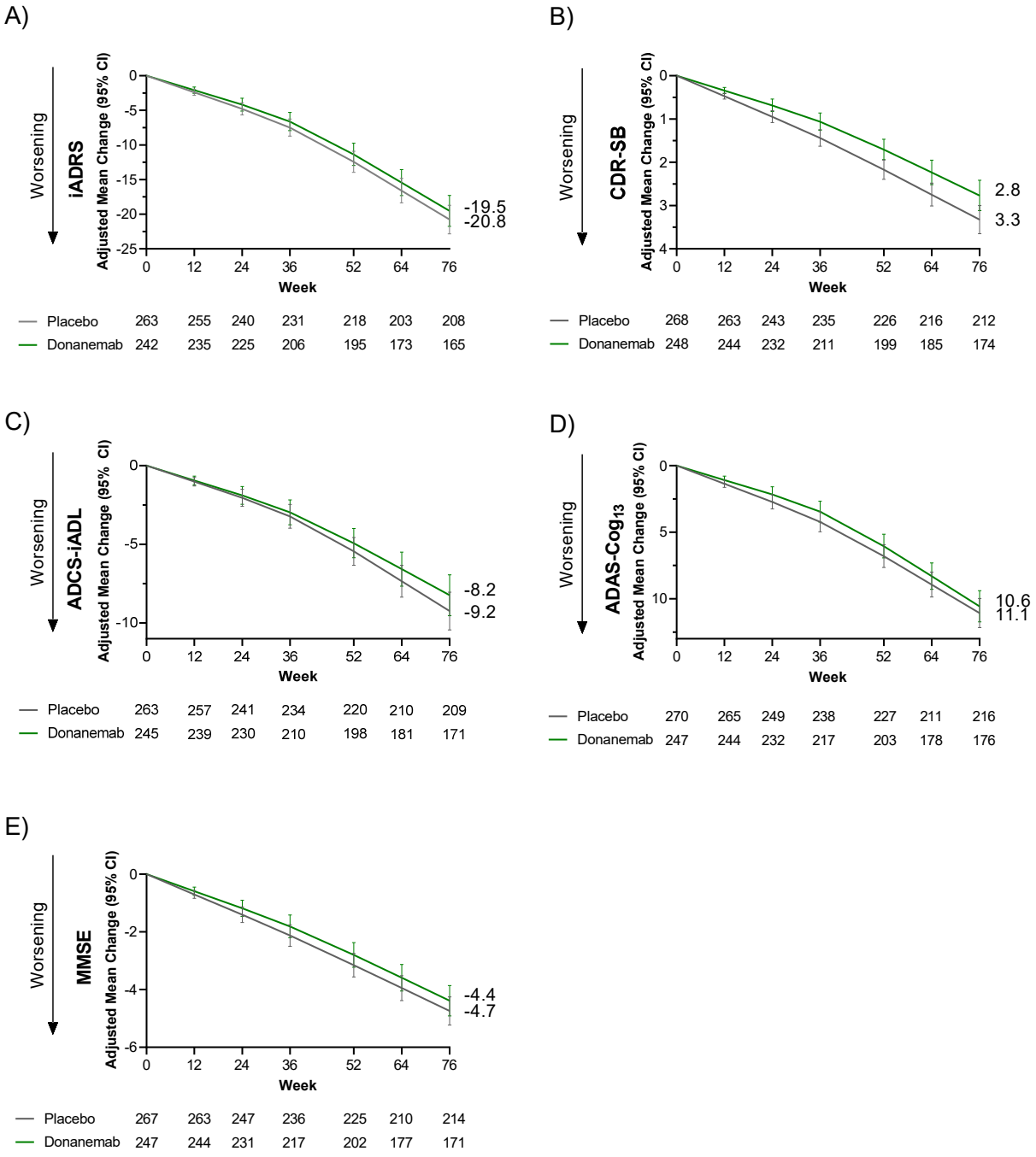
	N's (Placebo, Donanemab)	Adj. Mean Diff.	Percent Slowing (95% CI)
Age (years)			
≥75	(212, 205)	-0.55	28.8 (8.64, 49.02)
65-74	(215, 195)	-0.92	51.4 (28.46, 74.32)
<65	(32, 24)	0.18	-11.3 (-78.55, 55.90)
Sex			
Male	(217, 193)	-0.61	35.2 (12.07, 58.33)
Female	(242, 231)	-0.74	38.5 (19.28, 57.69)
Race			
Black/African American	(14, 14)	-0.38	26.6 (-82.33, 135.62)
Asian	(31, 37)	-0.06	5.2 (-75.00, 85.33)
White	(414, 373)	-0.73	38.7 (23.63, 53.82)
Ethnicity			
Hispanic/Latino	(16, 15)	-0.34	174.4 (-816.19, 1164.94)
Non-Hispanic/Latino	(308, 286)	-0.61	34.5 (17.11, 51.99)
Clinical Stage			
MCI (≥27)	(89, 94)	-0.40	44.1 (-19.45, 107.56)
Mild AD (20-26)	(296, 259)	-0.64	37.7 (18.44, 56.86)
Moderate AD (<20)	(74, 69)	-0.94	29.3 (9.67, 48.87)
ApoE4 Genotype			
Noncarrier	(116, 121)	-0.80	37.7 (13.25, 62.25)
Heterozygote	(255, 241)	-0.75	43.3 (22.28, 64.22)
Homozygote	(88, 62)	-0.20	11.9 (-26.51, 50.32)
Medication Use			
No	(206, 192)	-0.62	42.3 (14.49, 70.15)
Yes	(253, 232)	-0.73	34.3 (17.42, 51.13)
BMI (kg/m^2)			
<25	(207, 190)	-0.74	36.0 (16.36, 55.56)
25 to <30	(166, 161)	-0.59	35.7 (9.43, 61.96)
≥30	(86, 73)	-0.73	45.0 (4.67, 85.42)

D) CDR-SB: Combined Population



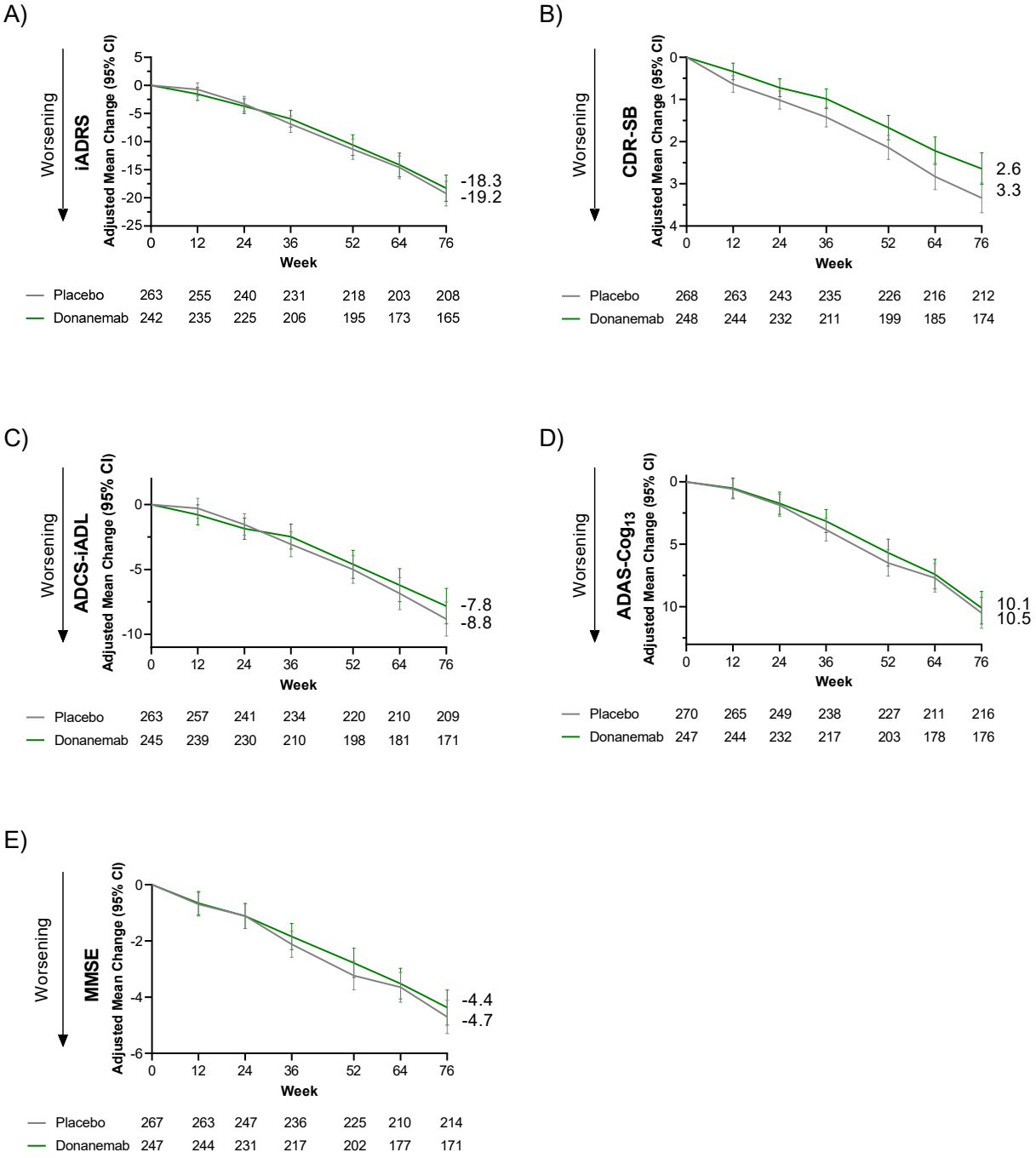
eFigure 10. NCS2 Analyses in the High-tau Population

Time course of change from baseline to 76 weeks in A) iADRS; % slowing (95%CI) 6.0 (-8.50, 20.59), B) CDR-SB (p-value <0.05 at 12 and 76 weeks, and <0.01 at 24, 36, 52, and 64 weeks); % slowing (95% CI) 16.8 (2.53, 31.04), C) ADCS-iADL; % slowing (95% CI) 10.9 (-8.25, 30.06), D) ADAS-Cog$_{13}$; % slowing (95% CI) 4.6 (-9.79, 18.99) and E) MMSE; % slowing (95% CI) 7.5 (-7.67,22.58) in the high-tau population. Data shown were analyzed using NCS2. The percent slowing (with 95% CI) across all clinical scales at 76w are shown on each graph. Number of participants in each group, at each time point are shown below each graph.
Abbreviations: ADAS-Cog$_{13}$, 13-item cognitive subscale of the Alzheimer's Disease Assessment Scale; ADCS-iADL, Alzheimer's Disease Cooperative Study – Instrumental Activities of Daily Living; CDR-SB, Clinical Dementia Rating Scale–Sum of Boxes; CI, confidence interval; iADRS, Integrated Alzheimer's Disease Rating Scale; MMSE, Mini–Mental State Examination; SE, standard error.



eFigure 11. MMRM Analyses in the High-tau Population

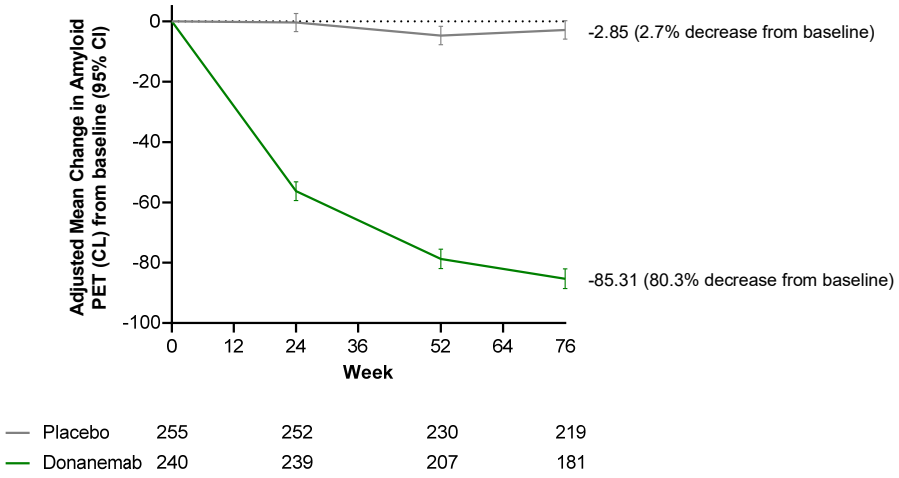
Time course of change from baseline to 76 weeks in A) iADRS; % slowing (95%CI) 4.9 (-11.24, 20.99), B) CDR-SB (p-value <0.05 at 12, 24, and 52 weeks, and <0.01 at 36, 64 and 76 weeks); % slowing (95% CI) 20.8 (5.88, 35.77), C) ADCS-iADL; % slowing (95% CI) 11.2 (-9.32, 31.80), D) ADAS-Cog_{13}; % slowing (95% CI) 3.9 (-12.46, 20.18) and E) MMSE; % slowing (95% CI) 7.1 (-10.18, 24.36) in the high-tau population. The percent slowing (with 95% CI) across all clinical scales at 76w are shown on each graph. Data shown were analyzed using MMRM. 95% CIs for LS mean changes were calculated with the normal approximation method. Number of participants in each group, at each time point are shown below each graph. Abbreviations: ADAS-Cog_{13}, 13-item cognitive subscale of the Alzheimer's Disease Assessment Scale; ADCS-iADL, Alzheimer's Disease Cooperative Study – Instrumental Activities of Daily Living; CDR-SB, Clinical Dementia Rating Scale–Sum of Boxes; CI, Confidence interval; iADRS, Integrated Alzheimer's Disease Rating Scale; MMSE, Mini–Mental State Examination; SE, standard error.



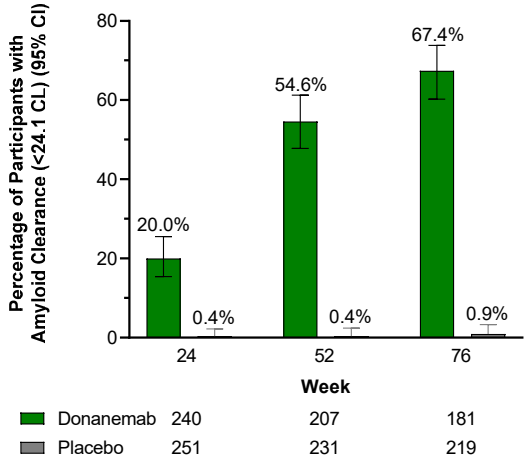
eFigure 12. Biomarkers in the High-tau Population

A) Time course of change from baseline to 76 weeks in brain amyloid plaque (p-value <0.0001 for all time points. B) The percentage of participants who achieved amyloid clearance (<24.1 CL) at each time point (p-value <0.0001 for all time points). C) Time course of change from baseline to 76 weeks in plasma P-tau217 levels (p-value <0.001 at 12 weeks and <0.0001 for all subsequent time points). All data are from the high-tau population. Biomarker data shown were analyzed using MMRM. 95% CIs for LS mean changes were calculated with the normal approximation method. Number of participants in each group, at each time point, are shown below each graph. Abbreviations: CDR-G, Clinical Dementia Rating Scale–Global; CL, Centiloids; CI, confidence interval; PET, positron emission tomography; P-tau217, phosphorylated tau 217; SE, standard error

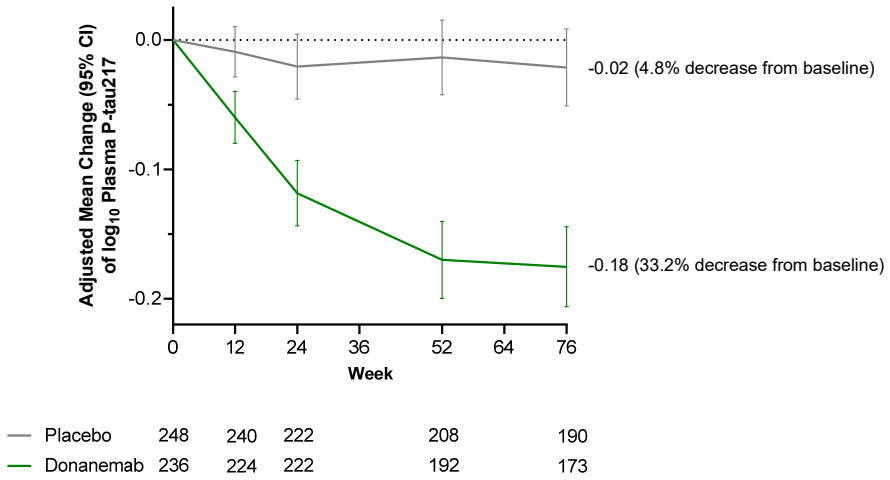
A)



B)

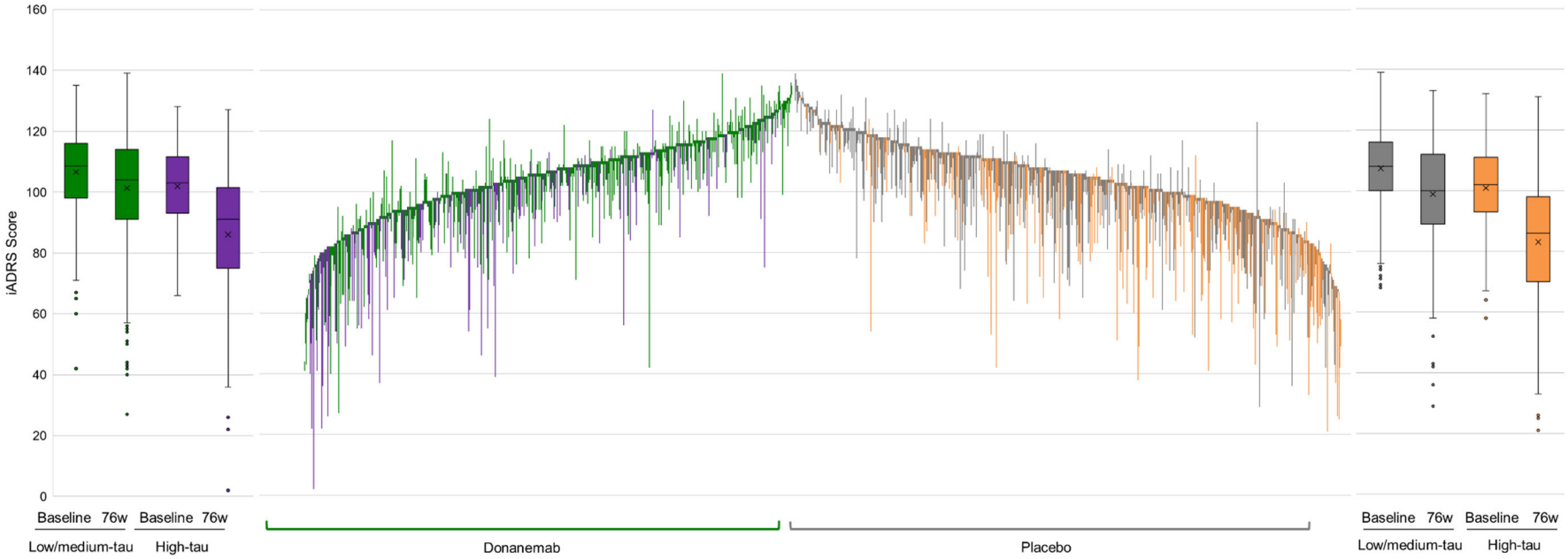


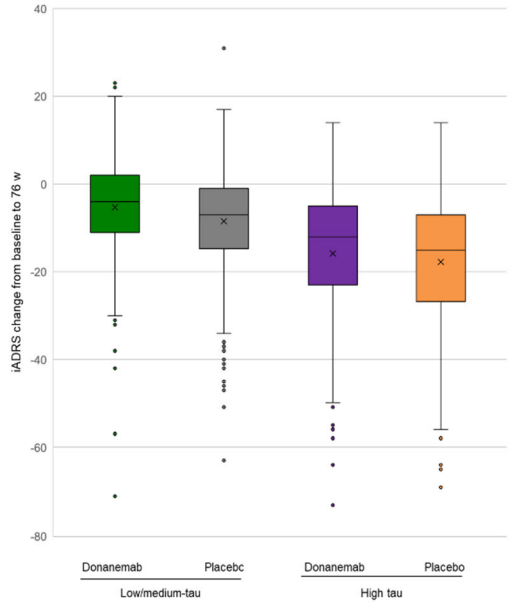
C)



eFigure 13. Baseline to 76w Change in Clinical Assessment of Individual Participants

Each vertical line represents an individual participant, which extends from the baseline clinical score to the score at 76w. Descending lines indicate the magnitude of disease progression, whereas ascending lines indicate improvement. Participants are arranged by ascending baseline value for participants who received donanemab and descending order for participants who received placebo. The ends of the box plots indicate the first and third quartile, with the middle line indicating the median and the x indicating the mean. Dots indicate extreme values. Abbreviations: iADRS, Integrated Alzheimer's Disease Rating Scale; Med. Medium; w, weeks





eMethods

eMethods 1. Protocol or Study Adjustments

eMethods 1A. Protocol Amendment History

Protocol Amendments	Substantial Changes
AACI (a) Dec 2020	In the original protocol, participants on the donanemab group were planned to receive 1400 mg every 4 weeks. Amendment (a) added a titration period of 700 mg for the first 3 doses due to higher-than-anticipated serious ARIA-E events relative to Phase 2.
AACI (b) Feb 2021	The amendment adapted Protocol AACI from a Phase 2 study to a Phase 3 study. The significant changes included • increase in the sample size • inclusion of P-tau181 as a pre-screening assessment, and its removal as an eligibility criterion from screening, and • changed in the primary analysis from "CDR-SB in overall population or low/medium-tau population" to "iADRS in the low/medium-tau population." The goal of the AACI study became to confirm Phase 2 results.
AACI (c) Sep 2021	The amendment increased the sample size by approximately 300 participants and defined approximately 300 early enrolled participants as Cohort 1. Cohort 1 was planned to be unblinded to the sponsor to inform analyses of safety and efficacy of donanemab and planning of future studies in AD. Sites, participants, and study partners remained blinded. The plan to unblind Cohort 1 was eventually removed as part of Amendment e (mentioned below)[a].
AACI (d) Oct 2021	The significant changes included the following: • The amendment added a long-term extension phase to this study to further evaluate the efficacy and safety of donanemab over time. • The Week 4 MRI was initially conducted only in Japan until this protocol amendment (d), which added the Week 4 MRI globally. The Week 4 MRI was used to check for evidence of ARIA-E or -H and other clinically relevant safety findings. Unscheduled MRIs could be performed at the discretion of the investigator.
AACI (e) Nov 2022	This amendment removed references to Cohort 1 and Cohort 2 analyses. This amendment also updated the analysis method from Bayesian Disease Progression Model to NCS for the primary objective.

Abbreviations: AD = Alzheimer's disease; ARIA-E = amyloid-related imaging abnormalities–edema/effusions (also known as vasogenic edema); ARIA-H = amyloid-related imaging abnormalities–hemorrhage/hemosiderin deposition (including brain microhemorrhage and superficial siderosis); CDR-SB = Clinical Dementia Rating Scale – Sum of Boxes; iADRS = integrated Alzheimer's Disease Rating Scale; MRI = magnetic resonance imaging; NCS = natural cubic spline.

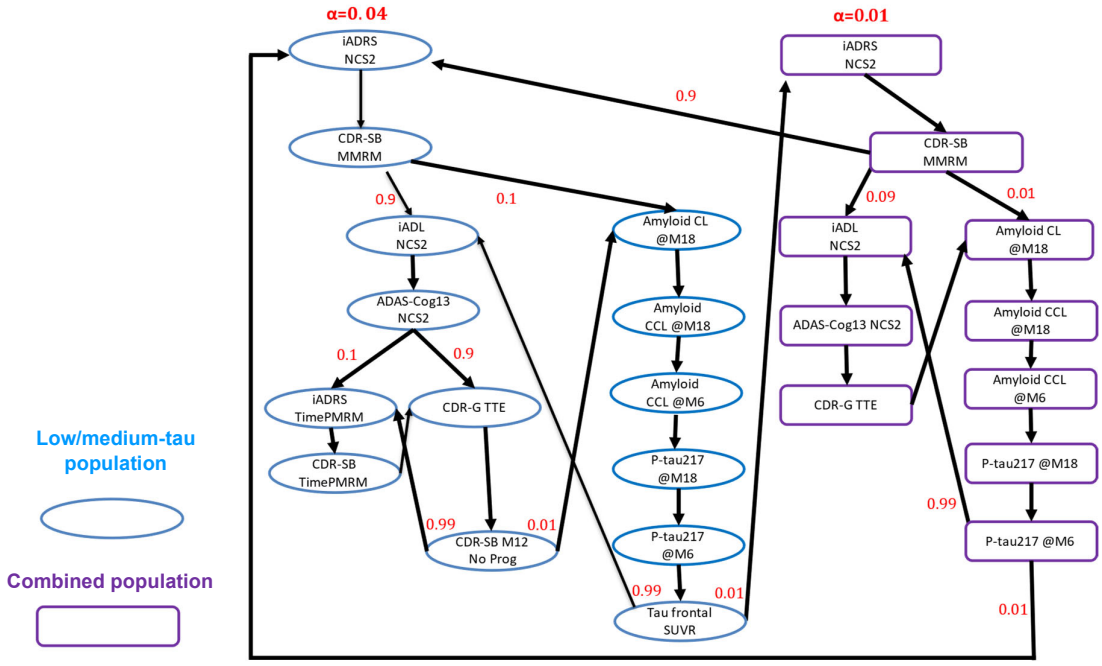
[a]Cohort 1 was never utilized and unblinding of Cohort 1 did not occur prior to final database lock.

eMethods 1B. Study Impacts from COVID-19

Start-up activities were delayed for about 4 to 6 weeks during April 2020, but most sites resumed activities in May 2020. Some sites, in most cases citing staffing difficulties, were delayed until fall or winter of 2020. Study AACI had first participant first visit on 19 June 2020 and was fully enrolled on 05 November 2021. Since Study AACI began after onset of the COVID-19 pandemic, elements intended to mitigate the impact of COVID-19 were built into the protocol or subsequent amendments. No protocol amendments or addenda were implemented as a result of the COVID-19 pandemic. Adjustments in study procedures included site visits conducted over telephone to collect preexisting conditions and adverse events, concomitant medications, cognitive assessments (Alzheimer's Disease Cooperative Study – Activities of Daily Living Inventory (ADCS-iADL), Clinical Dementia Rating Scale, Quality of Life in Alzheimer's Disease (Qol-AD), Resource Utilization in Dementia-Lite Version (RUD-Lite), self-harm supplement form, self-harm follow-up form, and Columbia-Suicide Severity Rating Scale (C-SSRS)). Temporary discontinuation from investigational product (IP) treatment was allowed if a short-term treatment with an excluded medication was necessary, secondary to hospitalization, personal or exceptional circumstances, or to evaluate the IP impact on an uncertain AE.

eMethods 2. Gating Scheme

Figure: Hypothesis testing scheme for controlling study-wise type I error rate at 2-sided 5%.



	Hypothesis to test
iADRS NCS2	iADRS score change LS mean differences at Week 76, tested with NCS model with 2 DF
CDR-SB MMRM	CDR-SB score change LS mean differences at Week 76, tested with MMRM
iADL NCS2	iADL score change LS mean differences at Week 76, tested with NCS model with 2 degree-of-freedom
ADAS-Cog13 NCS2	ADAS-Cog13 score change LS mean differences at Week 76, tested with NCS model with 2 DF
iADRS time-PMRM	Disease progression time saved at Week 76 as measured by iADRS, tested with time-PMRM model
CDR-SB time-PMRM	Disease progression time saved at Week 76 as measured by CDR-SB, tested with time-PMRM model
CDR-G TTE	Difference in hazard of progressing to first meaningful clinical worsening event defined by CDR-global score, tested with Cox proportional hazard model
CDR-SB wk 52 No Prog	Difference in probability of “no progression” as defined by CDR-SB at Week 52. Tested with GLIMM model
Amyloid CL	Amyloid Centiloid change LS mean difference at Week 76, tested with MMRM
Amyloid CCL @ Week 24	Probability of amyloid complete removal (Centiloid <24.1) among donanemab treated arm at Week 24, tested with binomial test
Amyloid CCL @ Week 76	Probability of amyloid complete removal (Centiloid <24.1) among donanemab treated arm at Week 76, tested with binomial test
P-tau217 @ Week 24	P-tau217 change LS mean difference at Week 24, tested with MMRM
P-tau217 @ Week 76	P-tau217 change LS mean difference at Week 76, tested with MMRM
Tau frontal SUVR	Tau PET frontal SUVR change LS mean difference at Week 76, tested with ANCOVA analysis

Abbreviations: ADAS-Cog13 = Alzheimer's Disease Assessment Scale – Cognitive subscale; ANCOVA = analysis of covariance; CDR-G = Clinical Dementia Rating Scale -Global Score; CDR-SB = Clinical Dementia Rating Scale – Sum of Boxes; CL = Centiloid; DF, degrees of freedom; iADRS = integrated Alzheimer's Disease Rating Scale; LS = least squares; PMRM = progression model with repeat measures; NCS2 = natural cubic spline model with 2 degrees of freedom; MMRM = mixed-effect model for repeated measures; PET = positron emission tomography; SUVR = standard uptake value ratio; TTE = time-to-event.

eMethods 3. Outcome Scales

Scale	Range	Score direction with *greater* disease severity	MWPC in those with mild cognitive impairment	MWPC in those with mild dementia due to AD	Additional Information
ADAS-Cog$_{13}$[2,3]	0-85	Higher	2	Not available	• Rater-administered, answered by participant/includes items rated by clinician • Assessment of cognition
ADCS-iADL[4,5]	0-59	Lower	Not available	Not available	• ADCS-ADL subset (items 6a and 7-23) • Rater-administered, answered by participant study partner • Assessment of function
CDR-SB[6-9]	0-18	Higher	1	2	• Semi-structured interview with participant and study partner/clinician rated • Integrated assessment of cognition and daily function
CDR-G[10,11]	0-3	Higher	No MWPC thresholds defined as any change indicates a change in disease stage. Any change is meaningful.	No MWPC thresholds defined as any change indicates a change in disease stage. Any change is meaningful.	• Semi-structured interview with participant and study partner/clinician rated • *Clinical Staging instrument. Stages*: 0=normal, 0.5=very mild dementia, 1=mild dementia, 2=moderate dementia, 3=severe dementia
iADRS[12-14]	0-144	Lower	-5	-9	• Mathematical derivation based on scores obtained from the ADAS-Cog13 and ADCS-iADL • Integrated assessment of cognition and daily function
MMSE[8,15]	0-30	Lower	-1	-2	• Rater-administered, answered by participant • Assessment of cognition

Abbreviations: AD = Alzheimer's Disease; ADAS-Cog$_{13}$ = Alzheimer's Disease Assessment Scale – Cognitive subscale; ADCS-ADL = Alzheimer's Disease Cooperative Study – Activities of Daily Living; ADCS-iADL = ADCS – instrumental ADLs; CDR-SB = Clinical Dementia Rating Scale – Sum of Boxes; CDR-G = CDR Global score; iADRS = integrated Alzheimer's Disease Rating Scale; MWPC = Meaningful Within Patient Change; MMSE = Mini-Mental State Examination

MWPC is a change that occurs in an individual patient over time and is different from between group differences which is the difference between two trial arms (commonly used to evaluate treatment effect). Between-group differences do not provide information on the magnitude of change experienced by an individual that is used to evaluate whether a meaningful score change is observed.[16]

eMethods 4. Tau PET

Study AACI enrolled low/medium and high-tau participants determined using 18F flortaucipir PET.[17] In more detail, tau PET categories at baseline were defined using an SUVr value and visual read:

- Low/medium-tau:

  1.10 ≤ SUVr ≤1.46, with a topographic deposition pattern consistent with moderate AD (AD+),
  or
  SUVr ≤1.46, with a topographic deposition pattern consistent with advanced AD (AD++), and

- High tau:

  SUVr >1.46, with a topographic deposition pattern consistent with either moderate (AD+) or advanced AD (AD++).

Patients with no or very low tau pathology were not included, because their expected rate of disease progression would not allow for reliable measurement of clinical decline or of study treatment effects within an 18-month study duration.

eMethods 5. P-tau217 Assay

The p-Tau Multi Analyte Assay (pTau-MAA) is a blood-based in vitro diagnostic test utilized by C2N Diagnostics to measure plasma P-tau217 in human plasma from trial participants. Liquid chromatography—mass spectrometry was used to separate, identify, and quantify the concentrations of tau peptides (tau amino acids 212 - 221) phosphorylated at Thr-217 (p-tau217, or p217) or not phosphorylated at Thr-217 (np-tau217, or np217) in human plasma. Tau was extracted from plasma by immunoprecipitation using a monoclonal tau antibody whose epitope is in proximity to the C-terminal p-tau217 and np-tau217 peptide sequences. The measurands are expressed as concentrations in pg/mL in whole numbers. The target peptide concentrations were calculated by the summation of peak areas from monitored product ions that result after fragmentation of their respective precursor ion. Precursor ions derive from endogenous and exogenous (added) stable isotope labeled peptides that correspond to phosphorylated and non-phosphorylated tau peptides that contain amino acids 212-221.

eMethods 6. Sensitivity Analyses

The primary efficacy outcome, iADRS, from the per-protocol dataset and from the dataset of those patients who remained in the study and on treatment through Week 76 (“completers” for placebo-controlled double blinded phase) were analyzed using the NCS2 analysis. The model setup and included covariates were the same as those described for NCS2. The “completers” also included baseline tau category as a fixed effect to the model applied to the combined population. ARIA-E censoring was also evaluated since events may lead to functional unblinding. To assess the impact of ARIA-E/IRR on treatment effect, the primary outcome measurement, iADRS was censored post the first occurrence of ARIA-E and/or IRR. The NCS2 model was applied to this censored dataset. The model setup and included covariates were the same as those described for NCS2.

eMethods 7. Subgroup Analyses

To assess the consistency of treatment effects across various demographic and baseline characteristics, subgroup analyses were conducted for iADRS and CDR-SB using NCS2 analyses with covariates as described in the manuscript methods plus additional covariates of subgroup by treatment, subgroup-by-basis expansion terms, and subgroup-by-basis expansion-by-treatment interactions. Except for medication use (yes/no), all subgroups were prespecified and included:

- Age group: <65, 65-74 versus ≥75 years
- Sex: female vs male
- Race: White, Black or African American, or Asian
- Ethnicity: Hispanic or Latino versus not Hispanic or Latino
- APOE4 Carrier Status: Carrier defined as E2/E4, E3/E4, or E4/E4 genotype; Non-Carrier defined as all other genotypes
- Number of APOE 4 alleles: 0, 1, or 2 E4 alleles
- Clinical staging at screening – MCI or mild AD
- Baseline brain tau burden category: low/medium-tau vs. high-tau
- Baseline tau SUVr tercile groups as defined by screening MUBADA SUVr for overall population: subjects with MUBADA SUVr <33% percentile, MUBADA SUVr within 33%-67% percentiles, and MUBADA SUVr >67% percentile.
- Baseline tau SUVr tercile groups as defined by screening MUBADA SUVr for loe/medium--tau level population: subjects with MUBADA SUVr <33% percentile, MUBADA SUVr within 33%-67% percentiles, and MUBADA SUVr >67% percentile.
- BMI: <25, 25- <30, ≥ 30

eMethods 8. Time-Based Analyses

Time-to-clinical worsening and Time progression models for the repeated measures (Time-PMRM)[18] were used to estimate the potential delay of disease progression in the donanemab recipients compared to the placebo group. A clinical worsening event was defined as meeting a scale (CDR-G, iADRS, CDR-SB) increase from baseline at 2 consecutive visits. A Cox proportional hazard model was fit to estimate the hazard ratio of progressing to clinical worsening between treatment arms. The model was used to estimate the time to first occurrence of the event and adjusted for baseline age, baseline CDR-GS, concomitant AChEI and/or memantine use at baseline (yes/no), and stratified by pooled investigator, and baseline tau category for overall population analysis. Progression to next clinical stage was defined as any increase in CDR-G at two consecutive visits from baseline. Meaningful within patient change (MWPC) was established as an iADRS change of ≥-5 and ≥-9 points and a CDR-SB change of ≥1 and ≥2 points for MCI due to AD and mild AD dementia respectively, at two consecutive visits from baseline. Analyses for CDR-G, iADRS, and CDR-SB were adjusted for baseline CDR-G, iADRS and CDR-SB, respectively.

The Time-PMRM was used to estimate the slowing of time progression of the disease due to donanemab treatment, or time progression in the placebo group. A natural cubic spline model with internal knots at each planned visit was used to interpolate the disease progression between the planned visits for the placebo arm. The donanemab trajectory was estimated by assuming it's mean trajectory at a given visit can be estimated by the mean disease progression of the placebo group at another time point, using a single parameter which assumes a proportional slowing in time of disease progression. The model was parameterized by a single parameter describing the proportional time slowing of the donanemab patients relative to placebo. The model adjusts for the same covariates as the primary efficacy analysis.

A generalized linear mixed model (GLMM) was also applied to estimate the probability of not-progressing by treatment group, where not progressing was defined at each postbaseline visit as a CDR-SB change from baseline score of 0 or an improved value. The model included the binary outcome of no progression (yes/no) at each postbaseline visit and the other baseline covariates as described in the primary efficacy analysis. The percent of patients who meet amyloid clearance (amyloid centiloid value < 24.1) at week 52 and 76 was calculated. A binomial test was fit to test whether the percentage is equal to 0.

References

1. Devous MD, Sr., Joshi AD, Navitsky M, et al. Test-Retest Reproducibility for the Tau PET Imaging Agent Flortaucipir F 18. *J Nucl Med*. Jun 2018;59(6):937-943. doi:10.2967/jnumed.117.200691
2. Mohs RC, Knopman D, Petersen RC, et al. Development of cognitive instruments for use in clinical trials of antidementia drugs: additions to the Alzheimer's Disease Assessment Scale that broaden its scope. The Alzheimer's Disease Cooperative Study. *Alzheimer Dis Assoc Disord*. 1997;11 Suppl 2:S13-21.
3. Rosen WG, Mohs RC, Davis KL. A new rating scale for Alzheimer's disease. *Am J Psychiatry*. Nov 1984;141(11):1356-64. doi:10.1176/ajp.141.11.1356
4. Galasko D, Bennett D, Sano M, et al. An inventory to assess activities of daily living for clinical trials in Alzheimer's disease. The Alzheimer's Disease Cooperative Study. *Alzheimer Dis Assoc Disord*. 1997;11 Suppl 2:S33-9.
5. Galasko D, Kershaw PR, Schneider L, Zhu Y, Tariot PN. Galantamine maintains ability to perform activities of daily living in patients with Alzheimer's disease. *J Am Geriatr Soc*. Jul 2004;52(7):1070-6. doi:10.1111/j.1532-5415.2004.52303.x
6. Hughes CP, Berg L, Danziger WL, Coben LA, Martin RL. A new clinical scale for the staging of dementia. *Br J Psychiatry*. Jun 1982;140:566-72. doi:10.1192/bjp.140.6.566
7. Morris JC. The Clinical Dementia Rating (CDR): current version and scoring rules. *Neurology*. Nov 1993;43(11):2412-4. doi:10.1212/wnl.43.11.2412-a
8. Andrews JS, Desai U, Kirson NY, Zichlin ML, Ball DE, Matthews BR. Disease severity and minimal clinically important differences in clinical outcome assessments for Alzheimer's disease clinical trials. *Alzheimers Dement (N Y)*. 2019;5:354-363. doi:10.1016/j.trci.2019.06.005
9. Lansdall CJ, McDougall F, Butler LM, et al. Establishing Clinically Meaningful Change on Outcome Assessments Frequently Used in Trials of Mild Cognitive Impairment Due to Alzheimer's Disease. *J Prev Alzheimers Dis*. 2023;10(1):9-18. doi:10.14283/jpad.2022.102
10. Cedarbaum JM, Jaros M, Hernandez C, et al. Rationale for use of the Clinical Dementia Rating Sum of Boxes as a primary outcome measure for Alzheimer's disease clinical trials. *Alzheimers Dement*. Feb 2013;9(1 Suppl):S45-55. doi:10.1016/j.jalz.2011.11.002
11. Coley N, Andrieu S, Jaros M, Weiner M, Cedarbaum J, Vellas B. Suitability of the Clinical Dementia Rating-Sum of Boxes as a single primary endpoint for Alzheimer's disease trials. *Alzheimers Dement*. Nov 2011;7(6):602-610 e2. doi:10.1016/j.jalz.2011.01.005
12. Wessels AM, Andersen SW, Dowsett SA, Siemers ER. The Integrated Alzheimer's Disease Rating Scale (iADRS) Findings from the EXPEDITION3 Trial. *J Prev Alzheimers Dis*. 2018;5(2):134-136. doi:10.14283/jpad.2018.10
13. Wessels AM, Siemers ER, Yu P, et al. A Combined Measure of Cognition and Function for Clinical Trials: The Integrated Alzheimer's Disease Rating Scale (iADRS). *J Prev Alzheimers Dis*. Dec 1 2015;2(4):227-241. doi:10.14283/jpad.2015.82
14. Wessels AM, Rentz DM, Case M, Lauzon S, Sims JR. Integrated Alzheimer's Disease Rating Scale: Clinically meaningful change estimates. *Alzheimers Dement (N Y)*. 2022;8(1):e12312. doi:10.1002/trc2.12312
15. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res*. Nov 1975;12(3):189-98. doi:10.1016/0022-3956(75)90026-6
16. FDA. *Patient-focused drug development public workshop: incorporating clinical outcome assessments into endpoints for regulatory decision-making*. 2019. December 6, 2019. https://www.fda.gov/media/132505/download
17. Mintun MA, Lo AC, Duggan Evans C, et al. Donanemab in Early Alzheimer's Disease. *N Engl J Med*. May 6 2021;384(18):1691-1704. doi:10.1056/NEJMoa2100708
18. Raket LL. Progression models for repeated measures: Estimating novel treatment effects in progressive diseases. *Stat Med*. Dec 10 2022;41(28):5537-5557. doi:10.1002/sim.9581