Donanemab in Early Symptomatic Alzheimer's Disease: Efficacy and Safety in TRAILBLAZER-ALZ 2, a Phase 3 Randomized Clinical Trial

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Disclosures

- Mark Mintun is an employee of Eli Lilly and Company and Avid Radiopharmaceuticals and minor shareholder of Eli Lilly and Company.
- Amyvid (Florbetapir F 18) was developed at Avid Radiopharmaceuticals and is marketed by Eli Lilly and Company as a radioactive diagnostic agent for Positron Emission Tomography (PET) imaging of the brain to estimate β-amyloid neuritic plaque density; safety and effectiveness of Amyvid (Florbetapir F 18) has not been established for predicting development of dementia or other neurologic conditions and monitoring responses to therapies.
- Tauvid (Flortaucipir F 18) is approved for use in the US with PET imaging of the brain to estimate the density and distribution of aggregated tau neurofibrillary tangles in adult patients with cognitive impairment who are being evaluated for Alzheimer's disease.
- All discussions refer to investigational purposes only.

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- This study was sponsored by Eli Lilly and Company.

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Today's program

Title	Presenter
TRAILBLAZER-ALZ 2: Clinical Background and Study Design	Paul R. Solomon
Donanemab in Early Symptomatic Alzheimer's Disease: Clinical Efficacy Results from TRAILBLAZER-ALZ 2	John R. Sims
Donanemab in Early Symptomatic Alzheimer's Disease: Safety Results from TRAILBLAZER-ALZ 2	Stephen Salloway
Donanemab in Early Symptomatic Alzheimer's Disease: Biomarker Results from TRAILBLAZER-ALZ 2	Oskar Hansson
The Clinical Relevance of the TRAILBLAZER-ALZ 2 Findings	Liana G. Apostolova
Panel Discussion and Question/Answer Session	Craig Richie, Mark Mintun (moderators)

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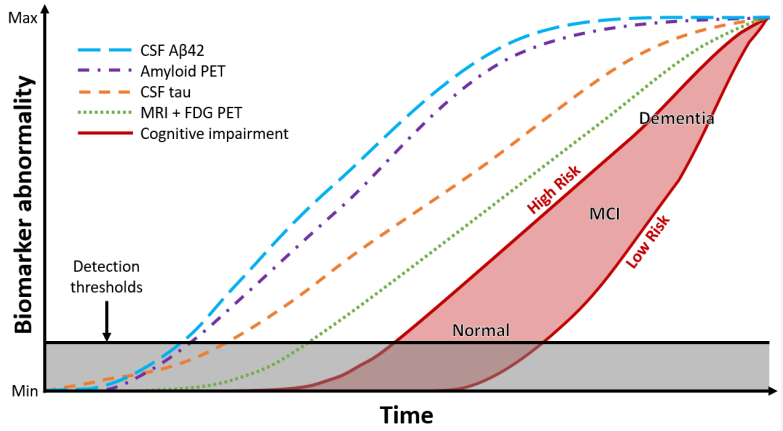
Donanemab background

Amyloid plaque accumulation in AD

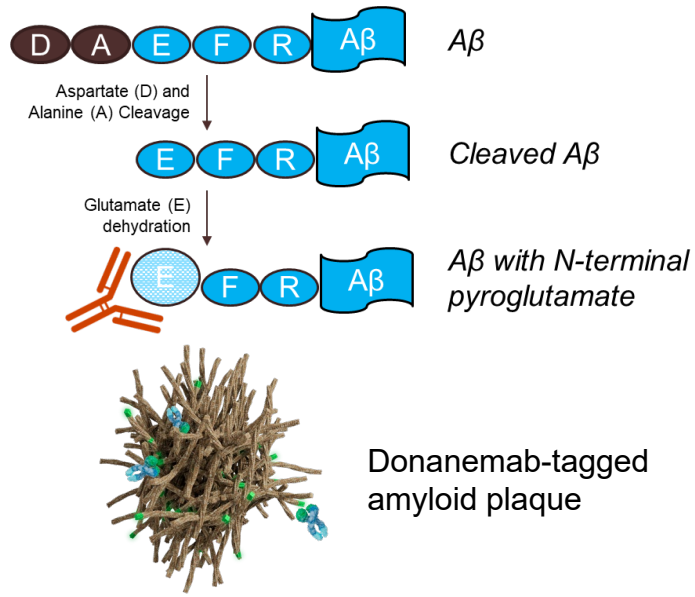
Accumulation of amyloid-β peptide in the form of amyloid plaques is an early and essential event in the onset of AD



Adapted from Selkoe & Hardy, EMBO Mol Med 2016

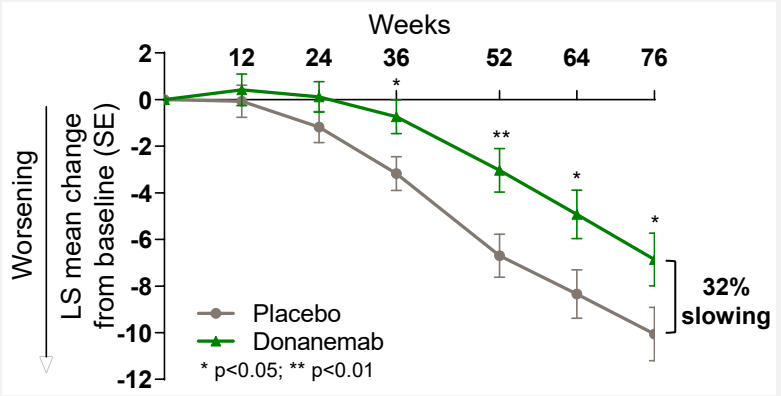
Donanemab Mechanism

Donanemab is an IgG1 monoclonal antibody directed against an insoluble, modified, N-terminal truncated form of amyloid-β (N3pG) present only in brain amyloid plaques

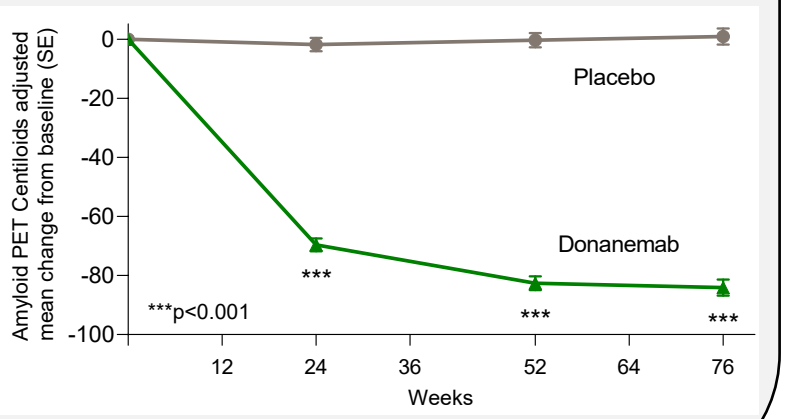


Phase 2 TRAILBLAZER-ALZ Results

Slowing Clinical Progression on iADRS



Rapid & Robust Amyloid Plaque Lowering



Adapted from Mintun et al, NEJM 2021

TRAILBLAZER-ALZ, NCT03367403. Abbreviations: Aβ=amyloid beta; AD=Alzheimer's disease; CSF=cerebrospinal fluid; FDG=fluorodeoxyglucose; iADRS=integrated Alzheimer's Disease Rating Scale; p=p-value; PET=positron emission tomography; LS=least square; MCI=mild cognitive impairment; MRI=magnetic resonance imaging; SE=standard error

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TRAILBLAZER-ALZ 2: Clinical Background and Study Design

Paul R. Solomon, PhD

Boston Center for Memory and Boston University Alzheimer's Disease Center, MA, USA

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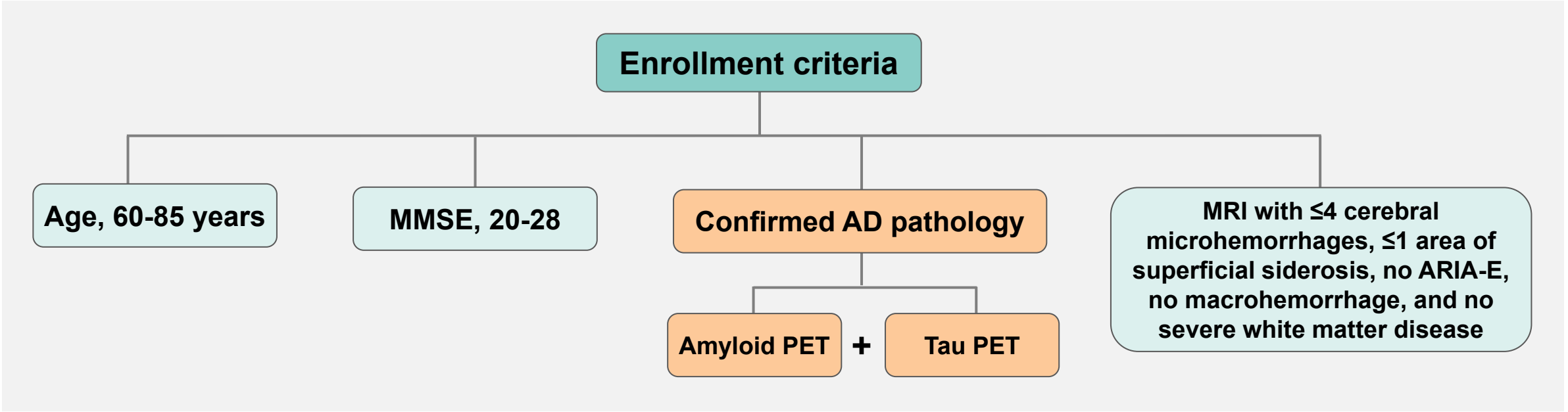
TRAILBLAZER-ALZ 2 study overview

- Phase 3, randomized, double-blind, placebo-controlled study to evaluate safety and efficacy of donanemab in individuals with early symptomatic AD (prodromal AD and mild dementia due to AD), with the presence of brain amyloid and tau pathologies



TRAILBLAZER-ALZ 2, NCT04437511. Abbreviations: AD=Alzheimer's disease; ARIA-E, amyloid-related imaging abnormalities-edema/effusions; MMSE=Mini-Mental State Examination; MRI=magnetic resonance imaging; PET=positron emission tomography

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Phase 3 TRAILBLAZER-ALZ 2 broadens global reach and patient population, allows flexibility in ARIA management

	TRAILBLAZER-ALZ	TRAILBLAZER-ALZ 2
Size	272 randomized	1736 randomized
Geographies	Canada and United States	Australia, Canada, Czech Republic, Japan, Netherlands, Poland, United Kingdom, United States
Tau PET inclusion criteria	Low-medium tau	Low-medium tau and high tau
Dosing	Step-down from 1400 mg to 700 mg or placebo based on amyloid PET level	No step-down to 700 mg (directly to placebo instead) based on amyloid PET level
ARIA-related discontinuation rules	Specific criteria for treatment discontinuation due to ARIA	Increased flexibility in treatment discontinuation due to ARIA
Clinical outcomes	iADRS, CDR-SB, ADAS-Cog_{13}, ADCS-iADL, MMSE	iADRS, CDR-SB, ADAS-Cog_{13}, ADCS-iADL, MMSE
Primary analysis method	Mixed-model repeated-measures	Natural cubic spline model
Extension study	Time delay to start of TB-EXT	Seamless extension of up to 78 weeks
Additional exposures	N/A	Open-label addendum (no tau exclusion criteria)

Abbreviations: ADAS-Cog_{13}=Alzheimer's Disease Assessment Scale–13-item Cognitive subscale; ADCS-iADL=Alzheimer's Disease Cooperative Study-instrumental Activities of Daily Living Inventory; ARIA=amyloid-related imaging abnormalities; CDR-SB=Clinical Dementia Rating Scale-Sum of Boxes; iADRS=Integrated Alzheimer's Disease Rating Scale; MMSE=Mini-Mental State Examination; N/A = not applicable; PET=positron emission tomography; TB-EXT=TRAILBLAZER-EXT (NCT04640077)

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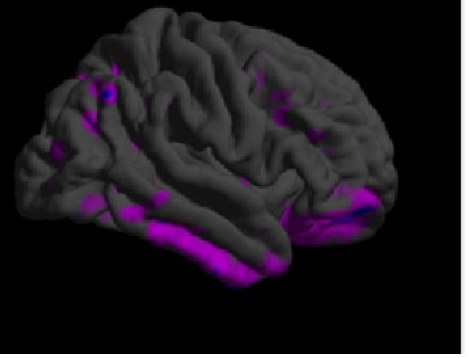
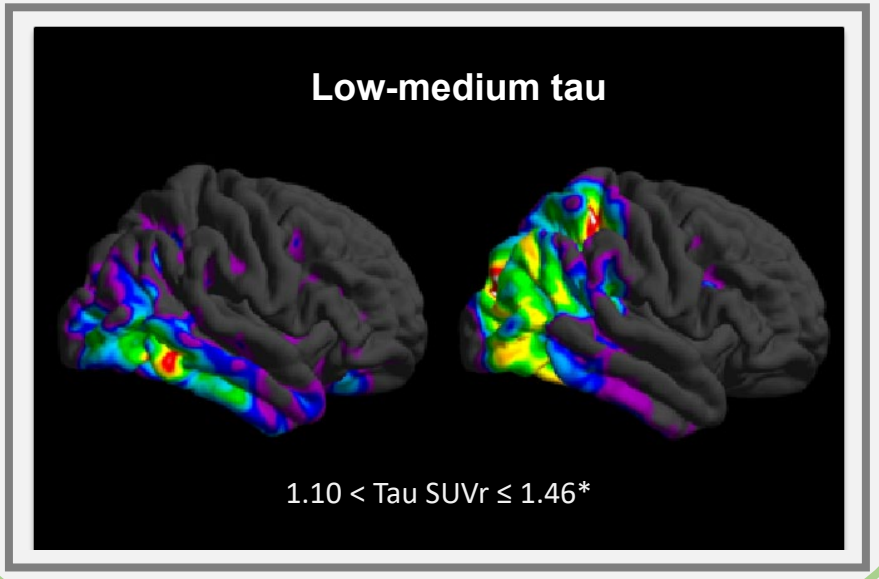
Enrolling participants based on tau pathology

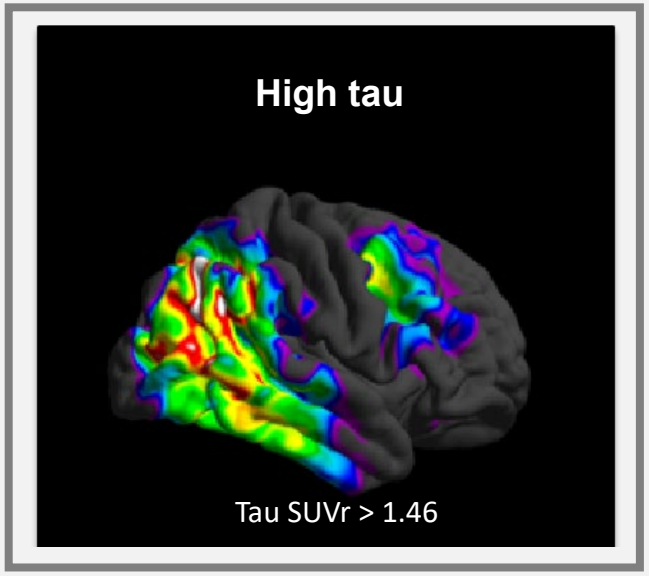
“No or very low tau”
not enrolled



Study Powered to Test
Low-medium Tau Population
(same as TRAILBLAZER-ALZ Phase 2)



Study allowed enrollment of high tau participants so efficacy could be tested in combined population (low-medium plus high tau)



*Visual interpretation also done and took precedent when highly discordant.

Abbreviations: MUBADA=multi-block barycentric discriminant analysis; PERSI=parametric estimation of reference signal intensity; SUVr=standardized uptake value ratio based on MUBADA region with PERSI reference region

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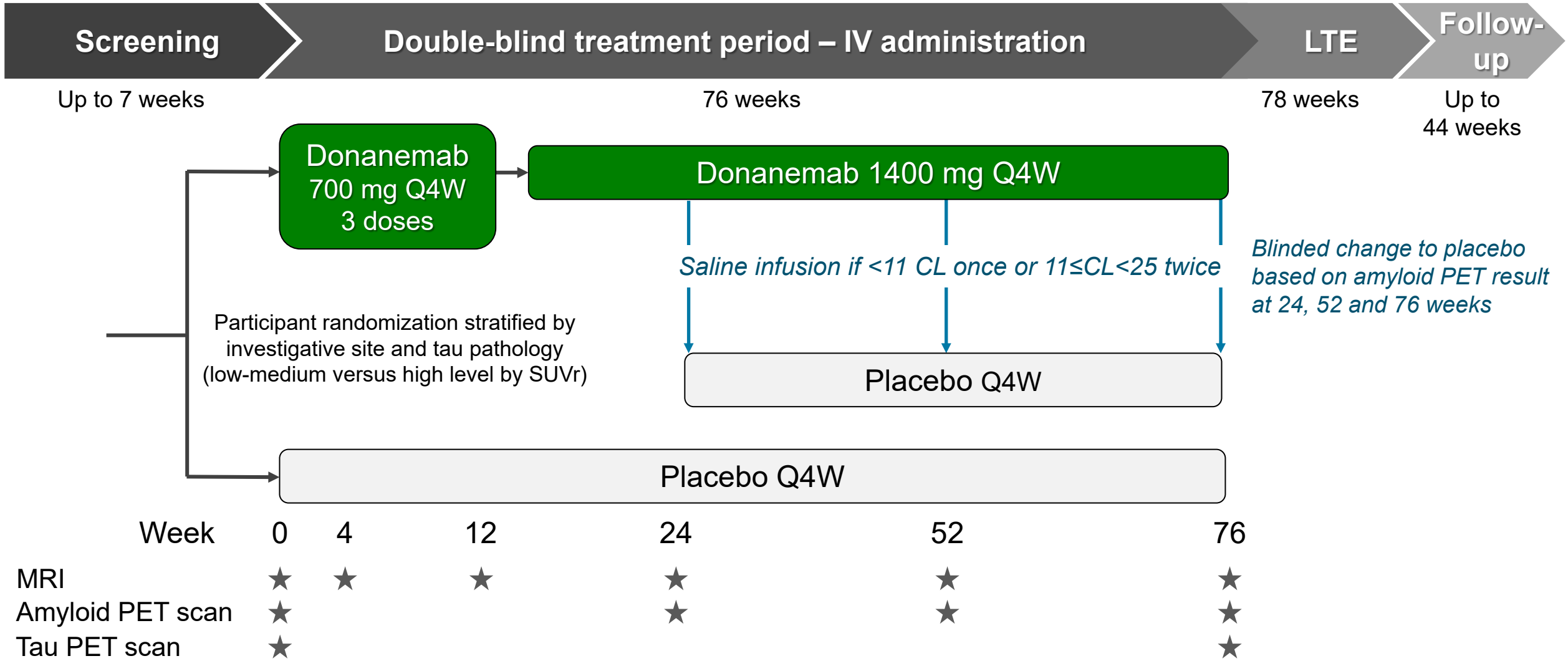
TRAILBLAZER-ALZ 2 study design



Abbreviations: CL=centiloids; IV=intravenous; LTE=long term extension; PET=positron emission tomography; Q4W=every 4 weeks; SUVr=standardized uptake value ratio

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Scales and biomarkers in graphical testing scheme

Primary Outcome

iADRS

Integrated assessment of cognition and daily function comprised of items from the ADAS-Cog_{13} and the ADCS-iADL, measuring global AD severity across the AD continuum

[scores range from 0-144 with lower score=greater impairment]

- Change from baseline to Week 76 in either low-medium tau pathology population or combined population

Gated Clinical Outcomes

CDR-SB

ADCS-iADL

ADAS-Cog_{13}

CDR-G

Gated Biomarker Outcomes

Amyloid PET

Plasma P-tau217

Tau PET

Abbreviations: AD=Alzheimer's disease; ADAS-Cog_{13}=Alzheimer's Disease Assessment Scale–13-item Cognitive subscale; ADCS-iADL=Alzheimer's Disease Cooperative Study-instrumental Activities of Daily Living Inventory; CDR-G=Clinical Dementia Rating-global; CDR-SB=Clinical Dementia Rating Scale-Sum of Boxes; iADRS=Integrated Alzheimer's Disease Rating Scale; PET=positron emission tomography; P-tau217=phosphorylated tau 217

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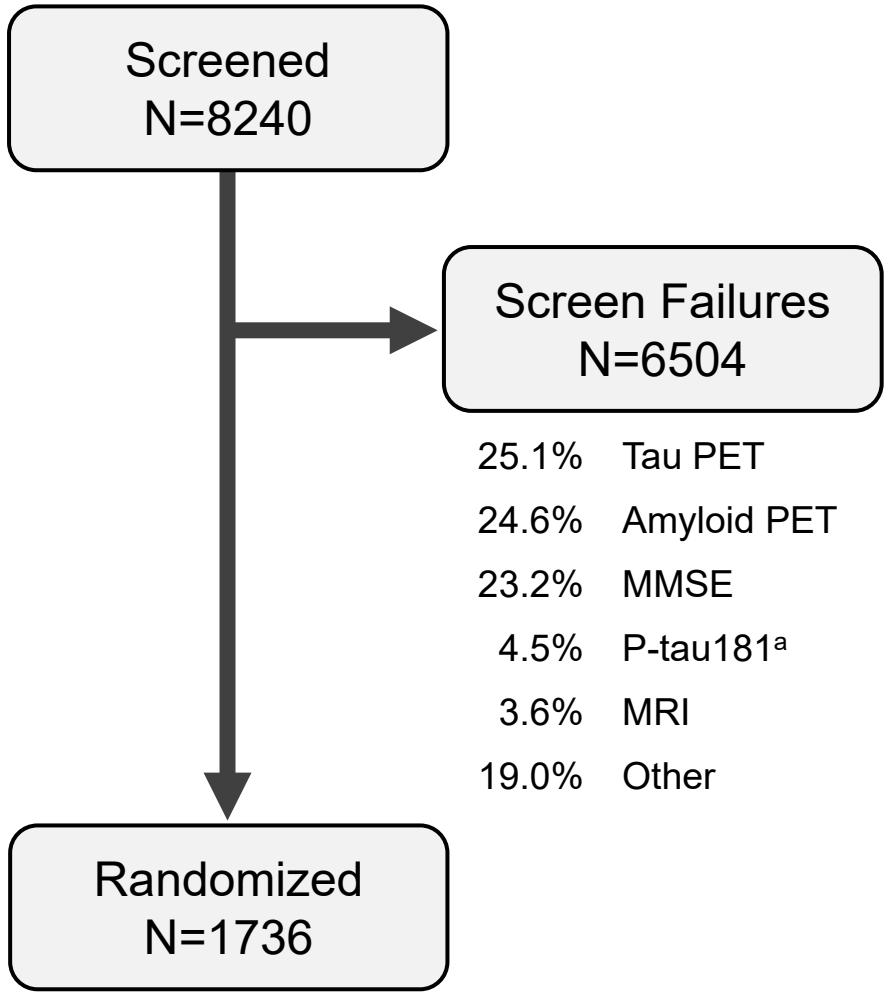
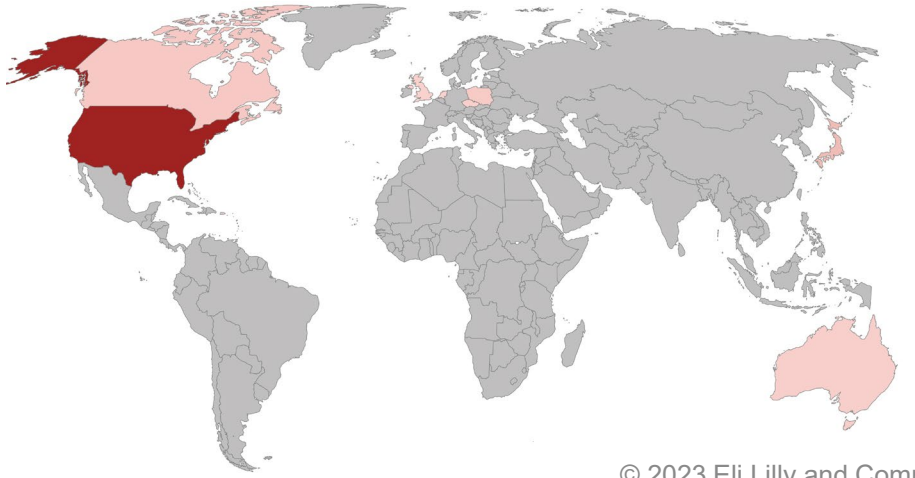
Screening and enrollment by geography



Country/Territory	# Sites	# Screened	# Randomized	%[b]
United States	188	6322	1241	71.5%
Japan	31	308	88	5.1%
Canada	17	679	137	7.9%
Poland	14	513	159	9.2%
Australia	9	44	17	1.0%
Czech Republic	6	53	22	1.3%
United Kingdom	4	222	39	2.2%
Netherlands	4	47	22	1.3%
Puerto Rico	4	52	11	0.63%
Total	**277**	**8240**	**1736**	



[a] Early version of protocol required presence of plasma P-tau181 before tau PET scan
[b] Percent of randomized
Abbreviations: MMSE=Mini-Mental State Examination; MRI=magnetic resonance imaging; PET=positron emission tomography; P-tau181=phosphorylated tau 181

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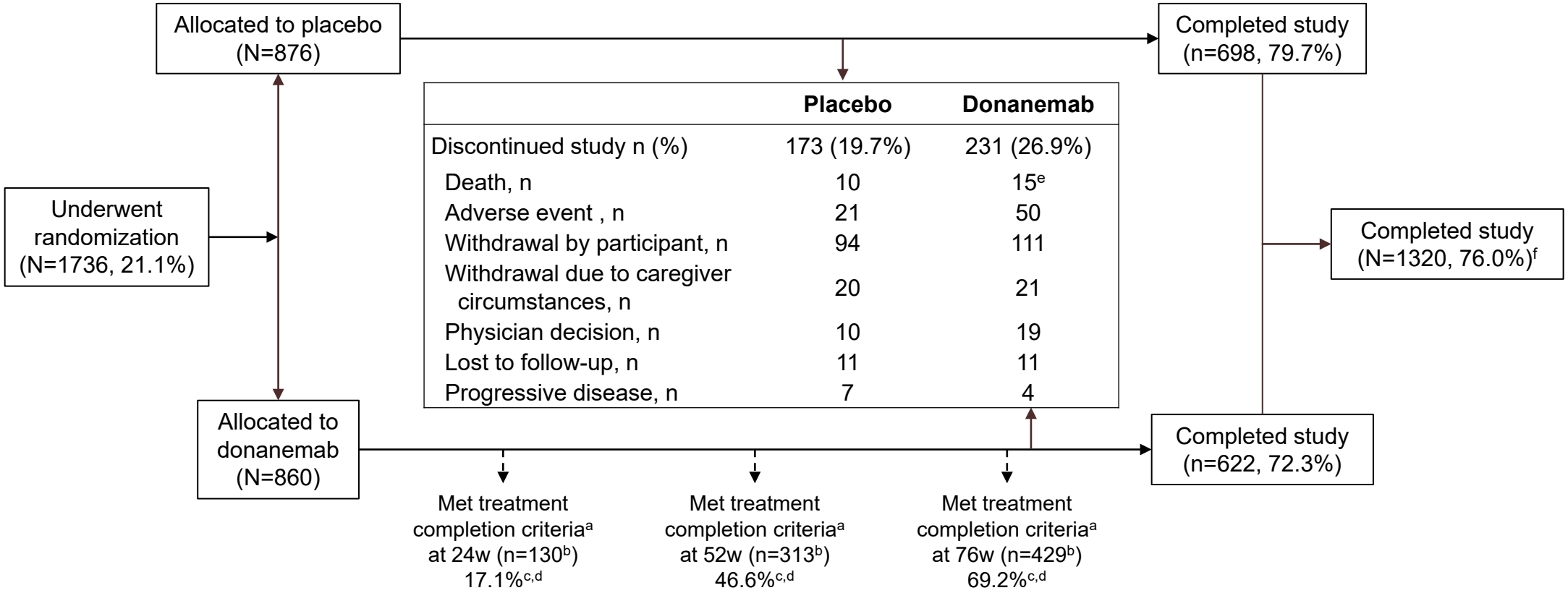
Participant disposition



	Placebo	Donanemab
Discontinued study n (%)	173 (19.7%)	231 (26.9%)
Death, n	10	15[e]
Adverse event , n	21	50
Withdrawal by participant, n	94	111
Withdrawal due to caregiver circumstances, n	20	21
Physician decision, n	10	19
Lost to follow-up, n	11	11
Progressive disease, n	7	4

[a] Treatment completion criteria: if the amyloid plaque level was less than 11 Centiloids on any one scan or 11≤CL<25 Centiloids on two consecutive scans.
[b] n=Number of participants who met treatment completion criteria and had a PET scan at the visit. Note: Dashed lines indicate these participants were included in the discontinuation and completion boxes for the donanemab group.
[c] Percentage calculated as n/number of participants with a PET scan at visit: n=761 at 24w, n=672, at 52w, and n=620 at 76w.
[d] Corresponding number of participants and percentages for the low-medium tau population were (n=106) 20.3% at 24w; (n=241) 51.9% at 52w; and (n=321) 73.5% at 76w.
[e] One additional death occurred after treatment completion and in the follow-up period.
[f] n=7 donanemab-treated participants and n=5 placebo-treated participants did not complete the final visit prior to the double-blind period data lock.

Abbreviations: N, n=number of participants in analysis population; n=number of participants within category; P-tau181=phosphorylated tau 181; PET=positron emission tomography; w=weeks

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Baseline demographics

	Low-medium Tau Population		Combined Population	
Demographic	**Placebo (N=594)**	**Donanemab (N=588)**	**Placebo (N=876)**	**Donanemab (N=860)**
Sex, n (%) female	321 (54.0)	325 (55.3)	503 (57.4)	493 (57.3)
Age, mean (SD), in years	74.3 (5.8)	74.3 (5.7)	73.0 (6.2)	73.0 (6.2)
Race n (%)				
% Asian	38 (6.4)	48 (8.2)	47 (5.4)	57 (6.6)
% Black or African American	17 (2.9)	17 (2.9)	21 (2.4)	19 (2.2)
% Black or African American (US only[a])	13 (3.1)	17 (4.1)	16 (2.5)	18 (2.9)
% White	539 (90.7)	522 (88.8)	807 (92.1)	781 (90.9)
% American Indian or Alaska Native	0	1 (0.2)	0	2 (0.2)
% Multiple	0	0	1 (0.1)	0
Ethnicity[b], n (%) Hispanic/Latino	26 (6.3)	24 (5.8)	36 (5.7)	35 (5.7)
Education of ≥13 years, n (%)	421 (71.0)	407 (69.2)	637 (72.8)	606 (70.5)
***APOE* ε4 carrier, n (%)**	427 (72.3)	421 (71.7)	621 (71.2)	598 (69.8)
AChEI and/or memantine use, n (%)	341 (57.4)	332 (56.5)	538 (61.4)	521 (60.6)

Numbers of participants with non-missing data were used as denominators to calculate percentages.

[a] US population range of 415-417 for the low-medium tau population and 619-632 for the combined population.

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

Abbreviations: AChEI=acetylcholinesterase inhibitors; *APOE*=apolipoprotein E; N, n=number of participants; SD=standard deviation

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Baseline clinical and biomarker measures

	Low-medium Tau Population		Combined Population	
Scale/biomarker, mean (SD)	**Placebo (N=594)**	**Donanemab (N=588)**	**Placebo (N=876)**	**Donanemab (N=860)**
iADRS	105.5 (13.7)	105.7 (13.8)	103.6 (14.0)	104.1 (14.3)
ADAS-Cog$_{13}$	27.8 (8.4)	27.5 (8.5)	29.3 (8.9)	28.7 (8.8)
ADCS-iADL	48.4 (7.9)	48.1 (7.9)	47.8 (7.8)	47.8 (7.9)
ADCS-ADL	66.9 (8.5)	66.7 (8.5)	66.4 (8.3)	66.3 (8.6)
MMSE[a]	22.8 (3.8)	23.1 (3.6)	22.2 (3.9)	22.4 (3.8)
CDR-SB	3.7 (2.0)	3.7 (2.1)	3.9 (2.1)	4.0 (2.1)
CDR-G, n (%)				
0	3 (0.5)	2 (0.3)	4 (0.5)	2 (0.2)
0.5	387 (65.5)	382 (65.9)	532 (61.2)	514 (60.8)
Amyloid PET, in Centiloids[b]	100.9 (35.1)	102.4 (34.7)	101.6 (34.5)	103.5 (34.5)
Tau PET AD signature weighted SUVr[b,c]	1.21 (0.13)	1.21 (0.12)	1.35 (0.26)	1.34 (0.25)
Plasma P-tau217, in pg/mL	5.4 (11.3)	6.6 (17.7)	6.8 (15.4)	7.5 (18.5)

Numbers of participants with non-missing data were used as denominators to calculate percentages.

[a] Last non-missing MMSE score prior to or at the start of study treatment.

[b] Based on screening data.

[c] SUVr with respect to a reference signal intensity in white matter parametric estimation of reference signal intensity (PERSI)

Abbreviations: Alzheimer's Disease Assessment Scale–13-item Cognitive subscale; ADCS-ADL=Alzheimer's Disease Cooperative Study–Activities of Daily Living; ADCS-iADL=Alzheimer's Disease Cooperative Study–Instrumental Activities of Daily Living; CDR-G=Clinical Dementia Rating-global; CDR-SB=Clinical Dementia Rating Scale–Sum of Boxes; iADRS=Integrated Alzheimer's Disease Rating Scale; MMSE=Mini–Mental State Examination; N, n=number of participants; PERSI=parametric estimation of reference signal intensity; PET=positron emission tomography; P-tau217=phosphorylated tau 217; SD=standard deviation; SUVr=standardized uptake value ratio

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A range of comorbidities and concomitant medications allowed in TRAILBLAZER-ALZ 2 study

- Baseline comorbidities and concomitant medications were well balanced

Comorbidity[a,b] n (%)	Placebo N=874	Donanemab N=853
Hypertension	480 (54.9)	469 (55.0)
Mood disorders (anxiety/depression)	389 (44.5)	403 (47.2)
Arthritis/osteoarthritis	342 (39.1)	313 (36.7)
Malignant or unspecified tumors	206 (23.6)	177 (20.8)
Thyroid disease	172 (19.7)	158 (18.5)
Obesity	153 (17.5)	154 (18.1)
Diabetes	154 (17.6)	139 (16.3)
Acute myocardial infarction/ ischemic heart disease	111 (12.7)	108 (12.7)

[a] In ≥10% of participants in the donanemab group at baseline
[b] Based on MedDRA Standardized Medical Queries of medical history

Concomitant medication[c,d] n (%)	Placebo N=874	Donanemab N=853
Donepezil	429 (49.1)	418 (49.0)
COVID-19 vaccine	346 (39.6)	326 (38.2)
Acetylsalicylic acid	273 (31.2)	271 (31.8)
Colecalciferol	219 (25.1)	233 (27.3)
Atorvastatin	223 (25.5)	223 (26.1)
Memantine	231 (26.4)	208 (24.4)
Paracetamol	200 (22.9)	225 (26.4)

[c] In >25% of participants in either group at baseline
[d] Based on WHO Drug Preferred Terms

Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities; N, n=number of participants; WHO=World Health Organization

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Summary

- TRAILBLAZER-ALZ 2 is a phase 3 study designed to evaluate safety and efficacy of donanemab in individuals with early symptomatic AD with the presence of brain amyloid and tau pathology

- A total of 8240 individuals screened for the placebo-controlled component yielded 1736 randomized participants
  - Main reasons for screen failures were distributed evenly across MMSE, amyloid PET and tau PET

- Baseline characteristics were balanced across placebo and donanemab groups
  - The combined population showed greater impairment across all clinical assessments compared with the low-medium tau population

Abbreviations: AD=Alzheimer's disease; MMSE=Mini–Mental State Examination; PET=positron emission tomography

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Donanemab in Early Symptomatic Alzheimer's Disease: Clinical Efficacy Results from TRAILBLAZER-ALZ 2

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Eli Lilly and Company, Indianapolis, Indiana, USA

Alzheimer's Association International Conference (AAIC)
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Sponsored by Eli Lilly and Company

Disclosures

- John R. Sims is an employee of Eli Lilly and Company.
- Eli Lilly and Company has pending patent application(s) on the P-tau217 blood test used in this research.
- Amyvid (Florbetapir F 18) was developed at Avid Radiopharmaceuticals and is marketed by Eli Lilly and Company as a radioactive diagnostic agent for Positron Emission Tomography (PET) imaging of the brain to estimate β-amyloid neuritic plaque density; safety and effectiveness of Amyvid (Florbetapir F 18) has not been established for predicting development of dementia or other neurologic conditions and monitoring responses to therapies.
- Tauvid (Flortaucipir F 18) is approved for use with PET imaging of the brain to estimate the density and distribution of aggregated tau neurofibrillary tangles in adult patients with cognitive impairment who are being evaluated for Alzheimer's disease.
- All discussions refer to investigational purposes only.

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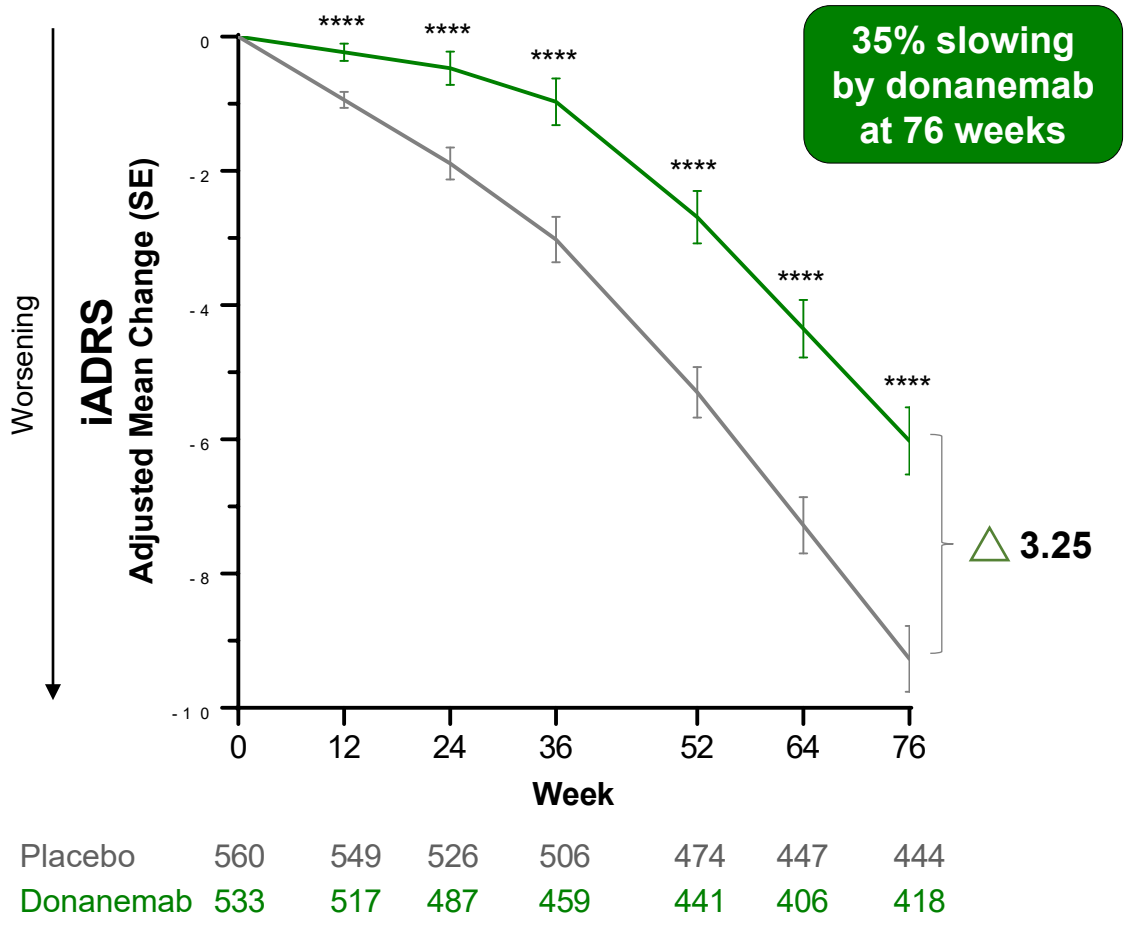
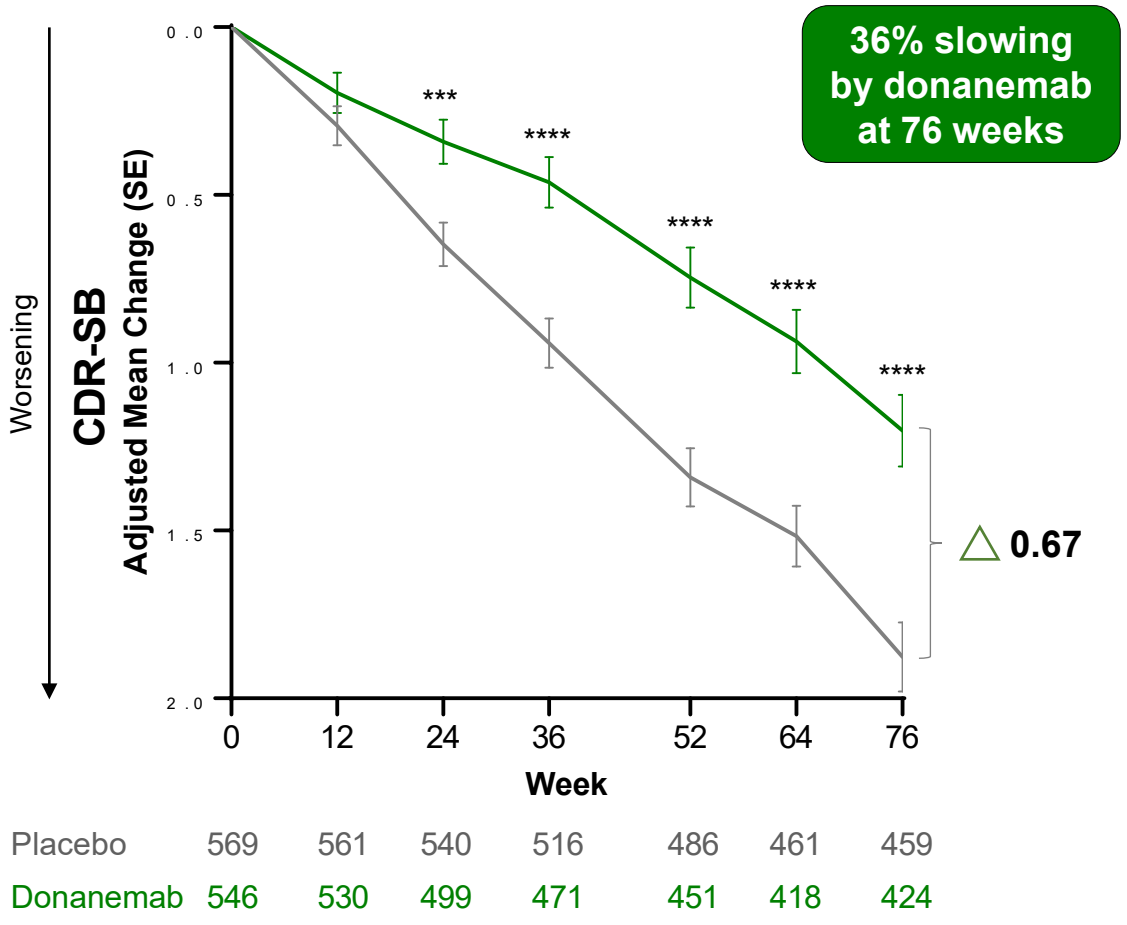
Phase 3 Primary Outcome: iADRS

Consistent with Key Secondary outcome on CDR-SB

iADRS: Low-medium Tau Population



CDR-SB: Low-medium Tau Population



TRAILBLAZER-ALZ 2 primary (iADRS) used the NCS model with 2 degrees of freedom adjusted for basis expansion terms (two terms), basis expansion term-by-treatment interaction, and covariates for age at baseline, pooled investigator, baseline tau level (overall model only), and baseline acetylcholinesterase inhibitor/memantine use. For CDR-SB: adjusted mean change from baseline, SE, 95% CI and p-value are derived using pre-specified mixed model repeated measures methodology with fixed factors for treatment, visit, treatment-by-visit interaction, and covariates for baseline score, baseline score-by-visit interaction, age at baseline, pooled investigator, and baseline acetylcholinesterase inhibitor/memantine use. * P<0.05, ** P<0.01, *** P<0.001, **** P<0.0001. Abbreviations: CDR-SB=Clinical Dementia Rating–Sum of Boxes; iADRS=Integrated Alzheimer's Disease Rating Scale; NCS=natural cubic spline; SE=Standard Error

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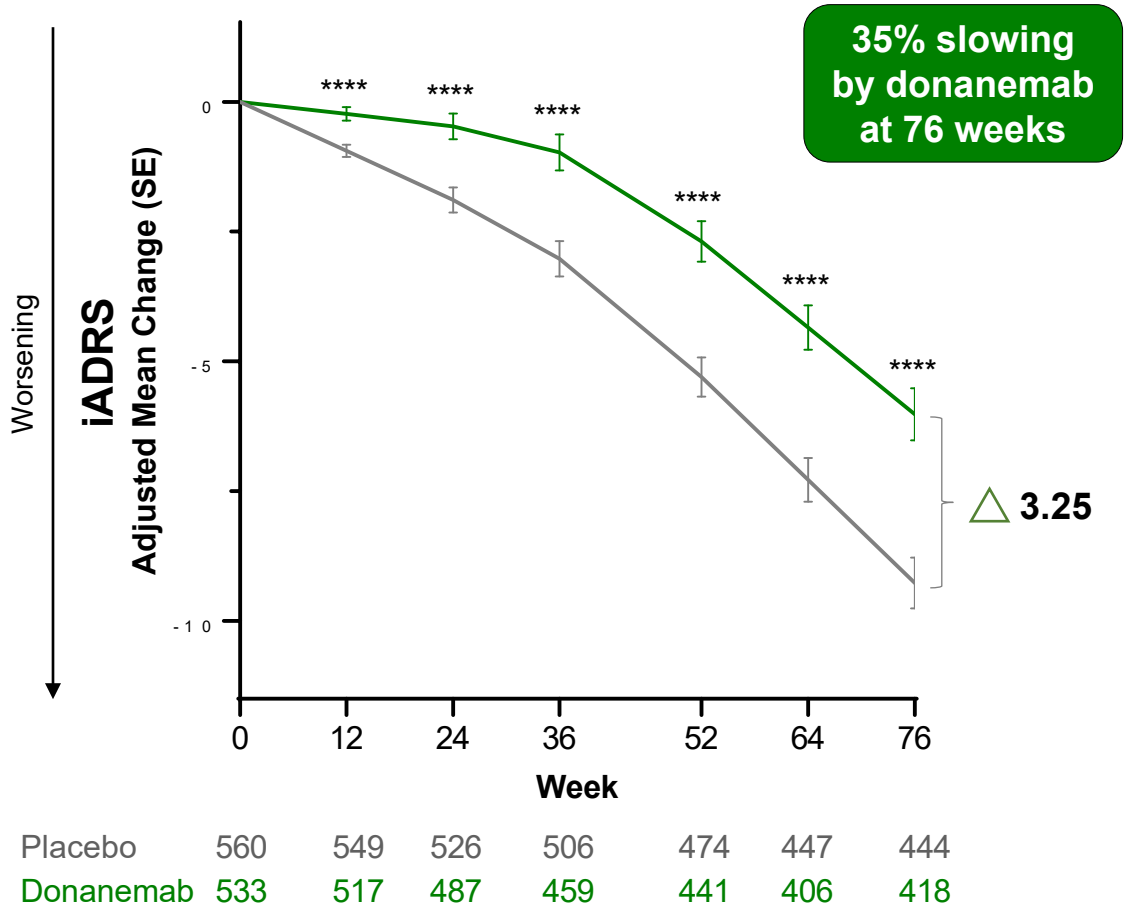
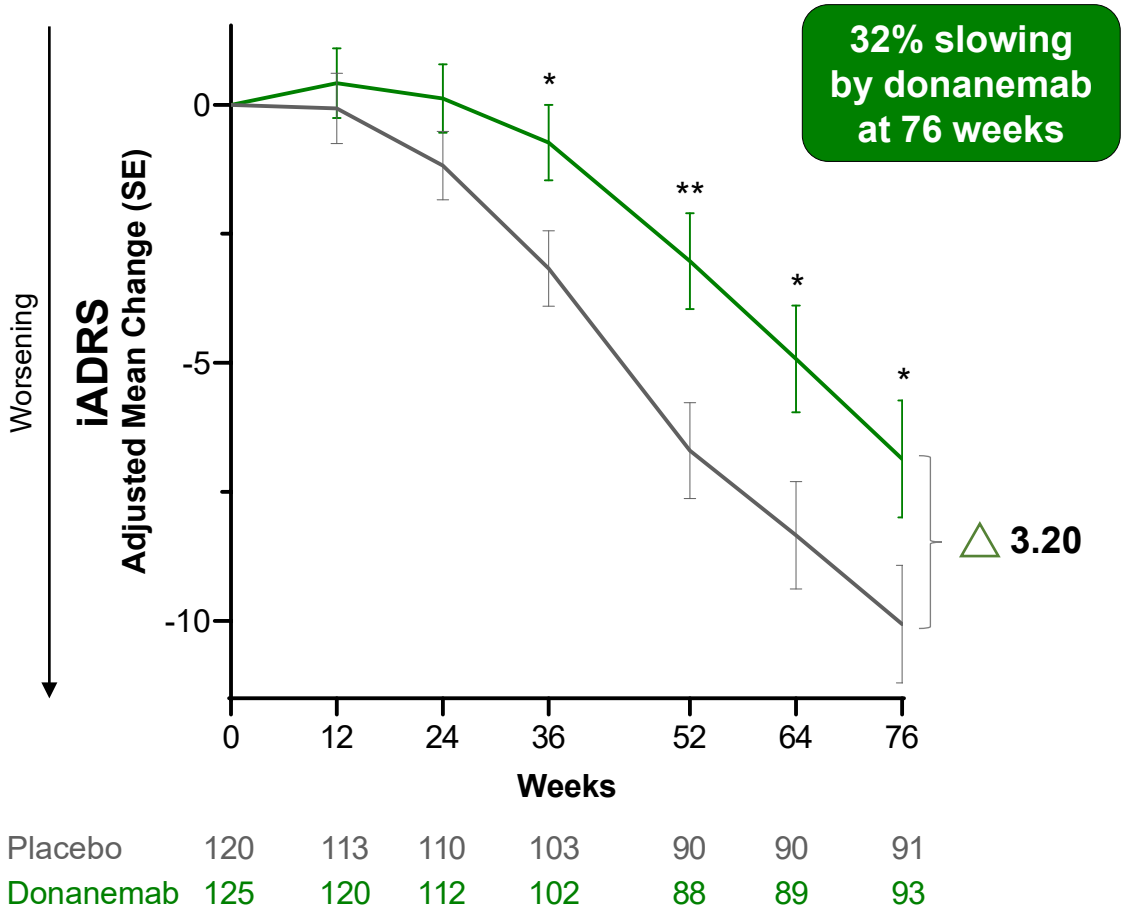
Phase 3 Primary Outcome: iADRS

Replicates Phase 2 Primary Outcome Result

TRAILBLAZER-ALZ 2: Low-medium Tau Population



TRAILBLAZER-ALZ 1: Phase 2 Trial



TRAILBLAZER-ALZ 2 primary analysis (iADRS) used the NCS model with 2 degrees of freedom adjusted for basis expansion terms (two terms), basis expansion term-by-treatment interaction, and covariates for age at baseline, pooled investigator, and baseline acetylcholinesterase inhibitor/memantine use. TRAILBLAZER-ALZ 1 primary analysis (iADRS) used mixed model repeated measures; the model included the following terms: treatment, visit, treatment-by-visit interaction, and covariates for baseline score, baseline score-by-visit interaction, age at baseline, pooled investigator, and baseline acetylcholinesterase inhibitor/memantine use. * P<0.05, ** P<0.01, *** P<0.001, **** P<0.0001. Abbreviations: iADRS=Integrated Alzheimer's Disease Rating Scale; NCS=natural cubic spline; SE=Standard Error

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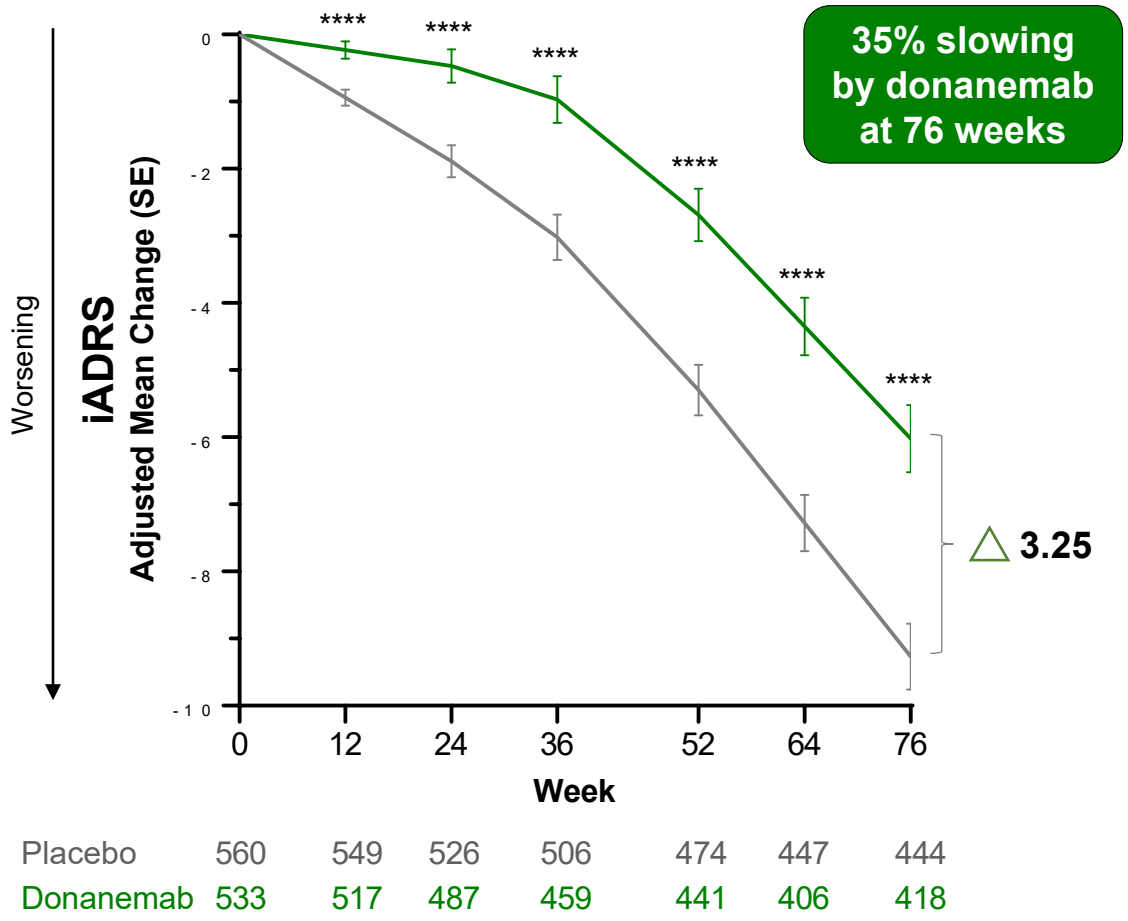
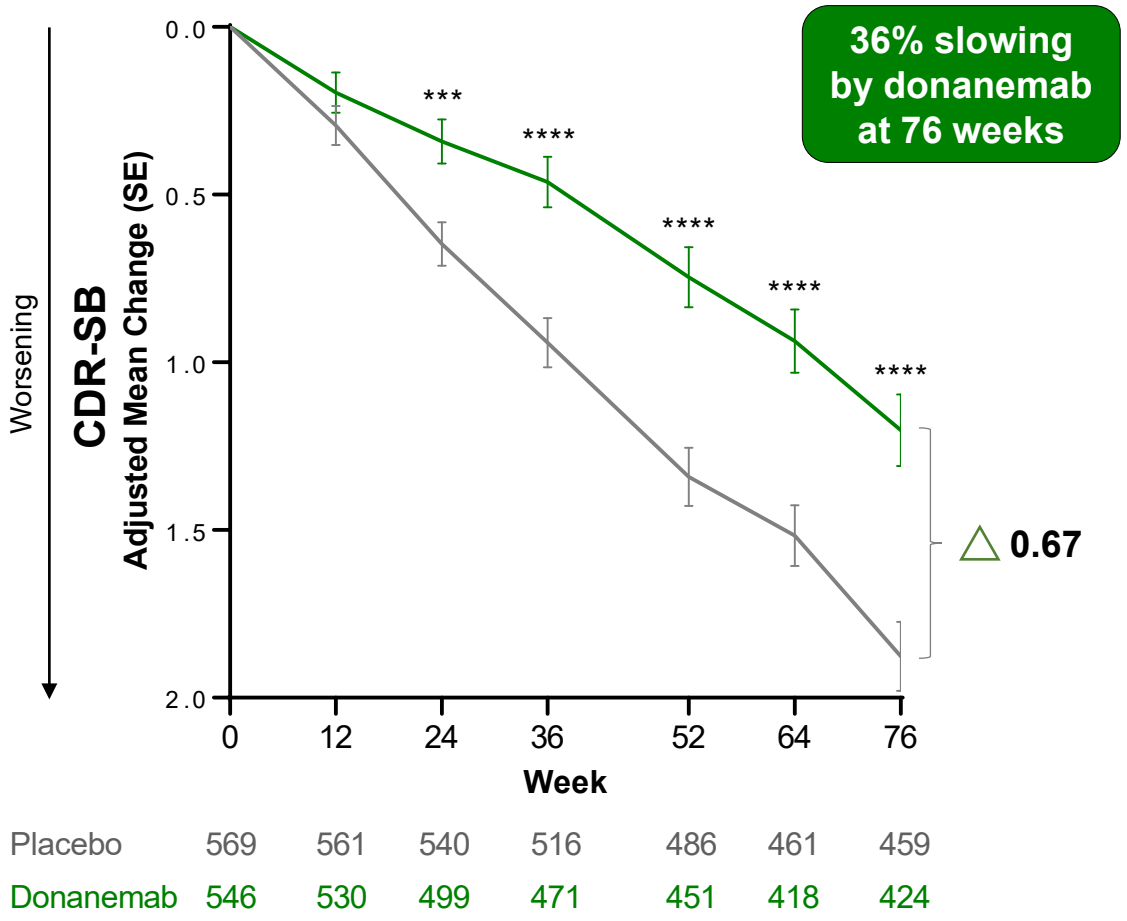
Phase 3 Primary Outcome: iADRS

Consistent with Key Secondary outcome on CDR-SB

iADRS: Low-medium Tau Population



CDR-SB: Low-medium Tau Population



TRAILBLAZER-ALZ 2 primary (iADRS) used the NCS model with 2 degrees of freedom adjusted for basis expansion terms (two terms), basis expansion term-by-treatment interaction, and covariates for age at baseline, pooled investigator, baseline tau level (overall model only), and baseline acetylcholinesterase inhibitor/memantine use. For CDR-SB: adjusted mean change from baseline, SE, 95% CI and p-value are derived using pre-specified mixed model repeated measures methodology with fixed factors for treatment, visit, treatment-by-visit interaction, and covariates for baseline score, baseline score-by-visit interaction, age at baseline, pooled investigator, and baseline acetylcholinesterase inhibitor/memantine use. * P<0.05, ** P<0.01, *** P<0.001, **** P<0.0001. Abbreviations: CDR-SB=Clinical Dementia Rating–Sum of Boxes; iADRS=Integrated Alzheimer's Disease Rating Scale; NCS=natural cubic spline; SE=Standard Error

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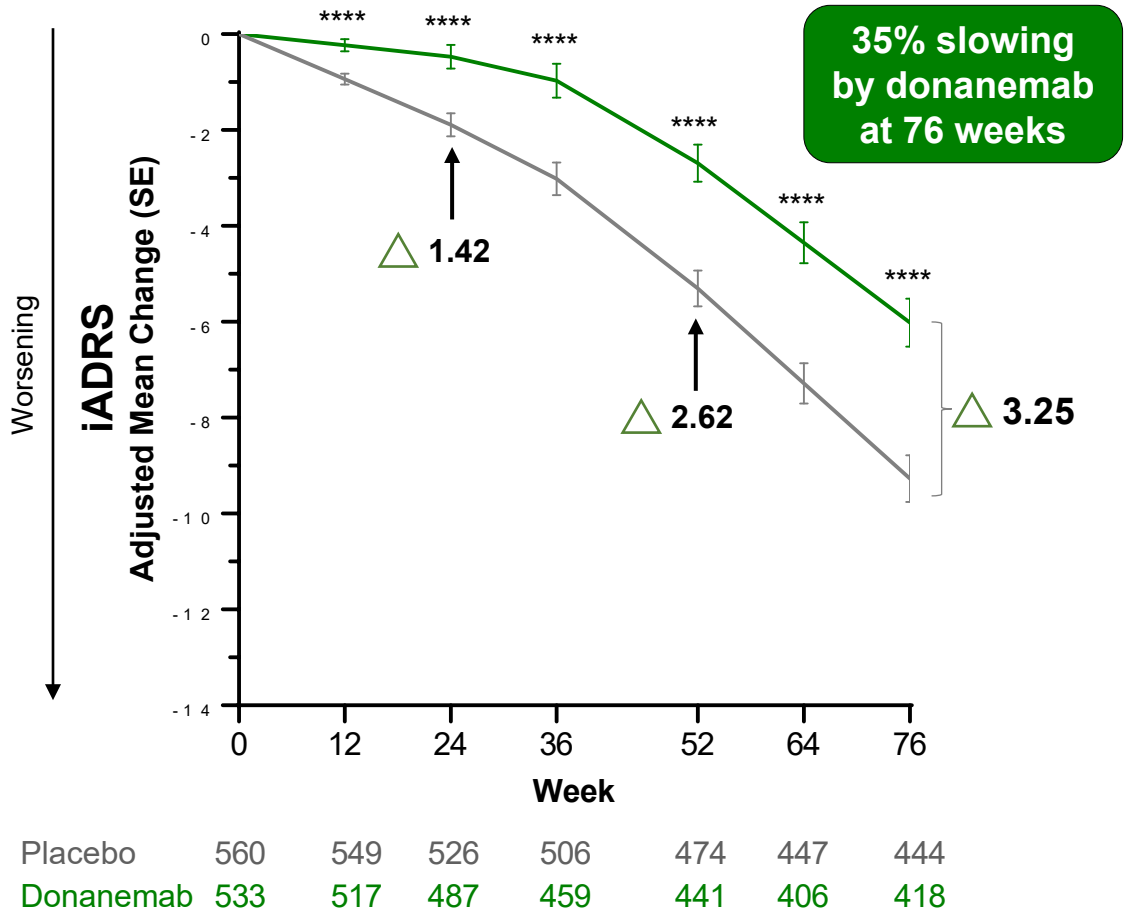
Phase 3 Primary Outcome: iADRS

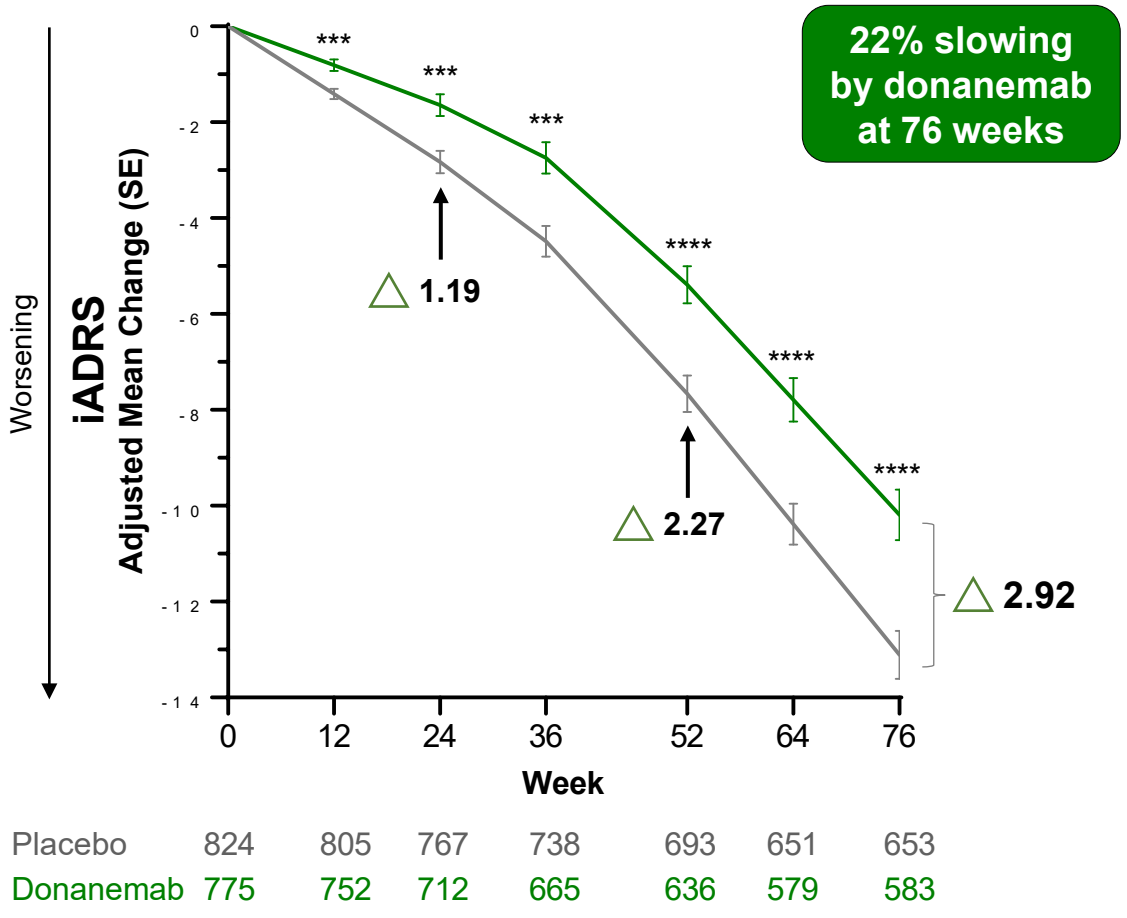
Both Populations Show Treatment Effect which Widens over Time

iADRS: Low-medium Tau Population



Placebo	560	549	526	506	474	447	444
Donanemab	533	517	487	459	441	406	418

iADRS: Combined Tau Population



Placebo	824	805	767	738	693	651	653
Donanemab	775	752	712	665	636	579	583

TRAILBLAZER-ALZ 2 primary analysis (iADRS) used the NCS model with 2 degrees of freedom adjusted for basis expansion terms (two terms), basis expansion term-by-treatment interaction, and covariates for age at baseline, pooled investigator, baseline tau level (Combined model only), and baseline acetylcholinesterase inhibitor/memantine use. * P<0.05, ** P<0.01, *** P<0.001, **** P<0.0001. Abbreviations: iADRS=Integrated Alzheimer's Disease Rating Scale; NCS=natural cubic spline; SE=Standard Error

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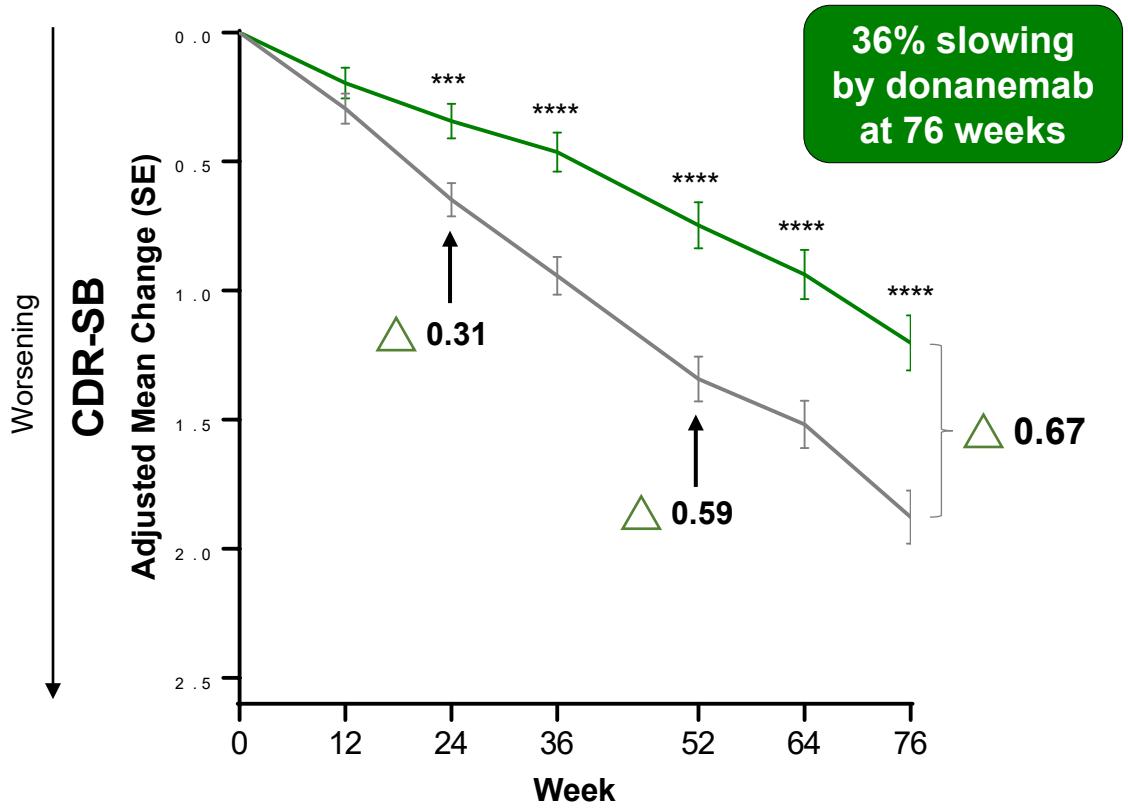
Key Secondary Outcome: CDR-SB

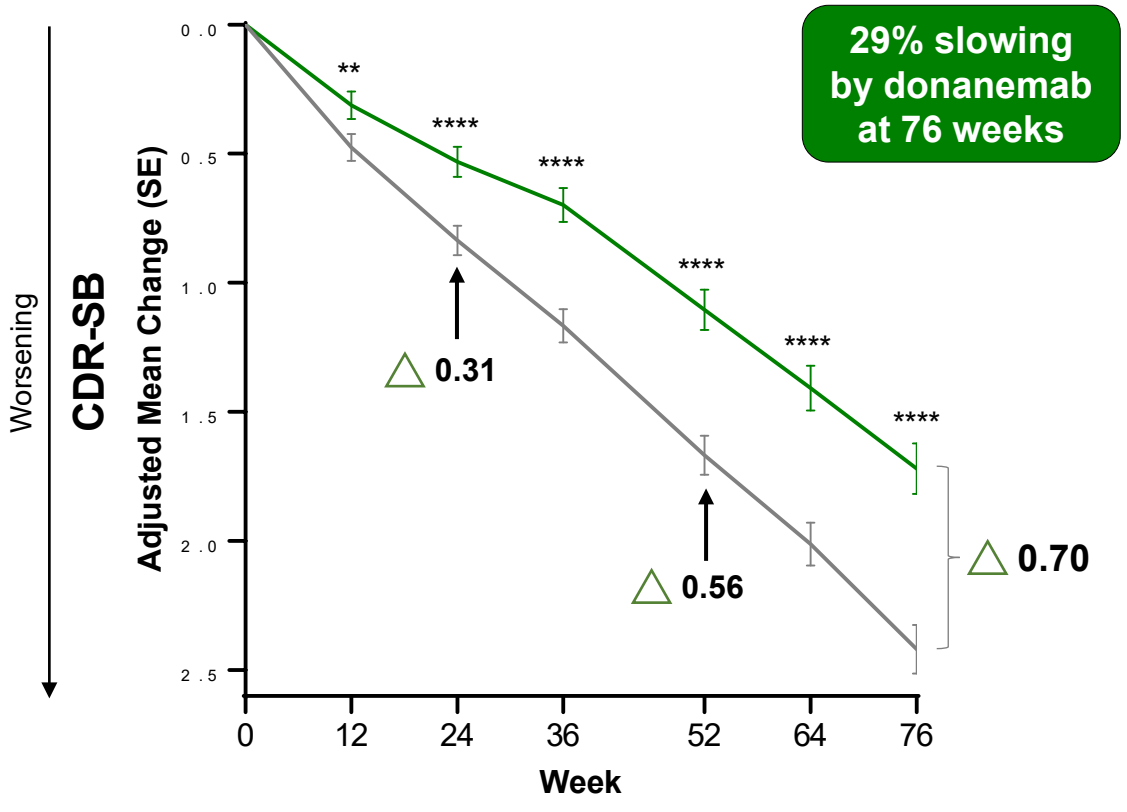
Both Populations Show Treatment Effect which Widens over Time

CDR-SB: Low-medium Tau Population



Placebo	569	561	540	516	486	461	459
Donanemab	546	530	499	471	451	418	424

CDR-SB: Combined Tau Population



Placebo	838	825	784	752	713	678	672
Donanemab	794	774	731	682	650	603	598

For CDR-SB: adjusted mean change from baseline, SE, 95% CI and p-value are derived using pre-specified mixed model repeated measures methodology with fixed factors for treatment, visit, treatment-by-visit interaction, and covariates for baseline score, baseline score-by-visit interaction, age at baseline, pooled investigator, baseline acetylcholinesterase inhibitor/memantine use and baseline tau level (Combined model only). ** P<0.01, *** P<0.001, **** P<0.0001. Abbreviations: CDR-SB=Clinical Dementia Rating–Sum of Boxes; SE=Standard Error

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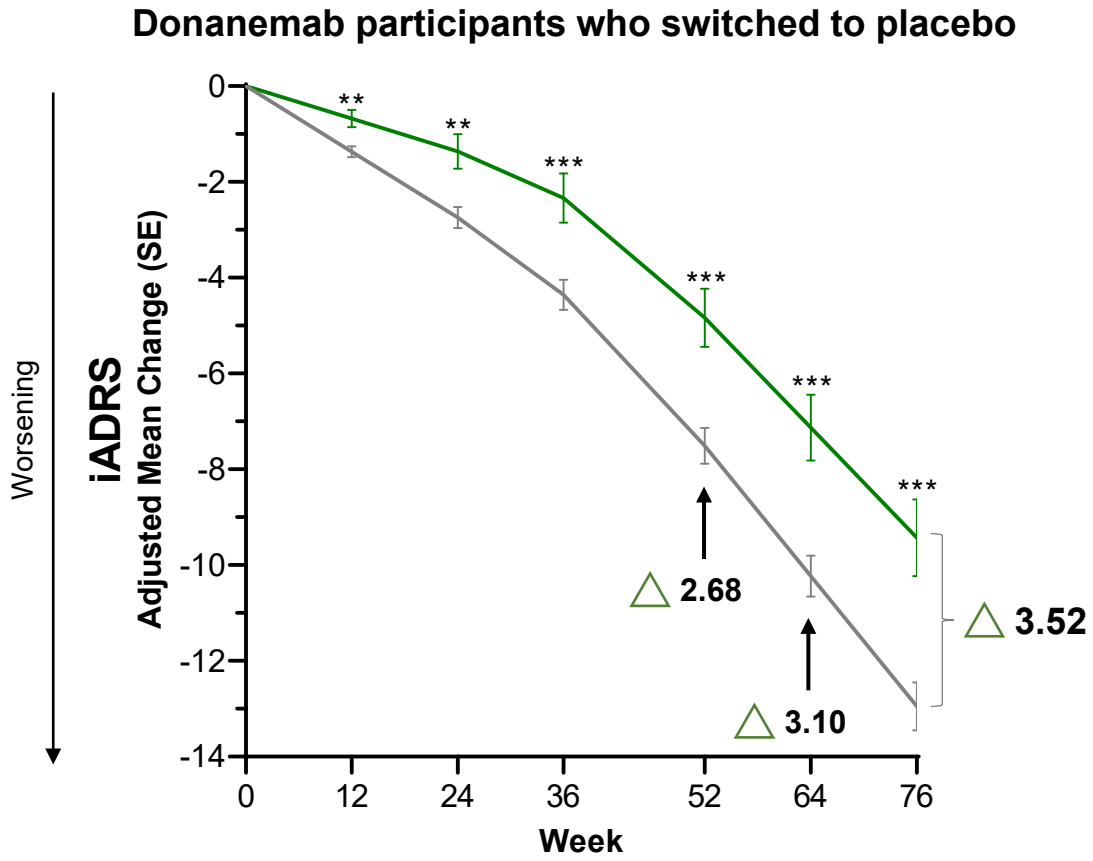
Treatment Effect Continues to Widen Even After Participants are Switched to Placebo Based on 6- or 12-Month PET Scan

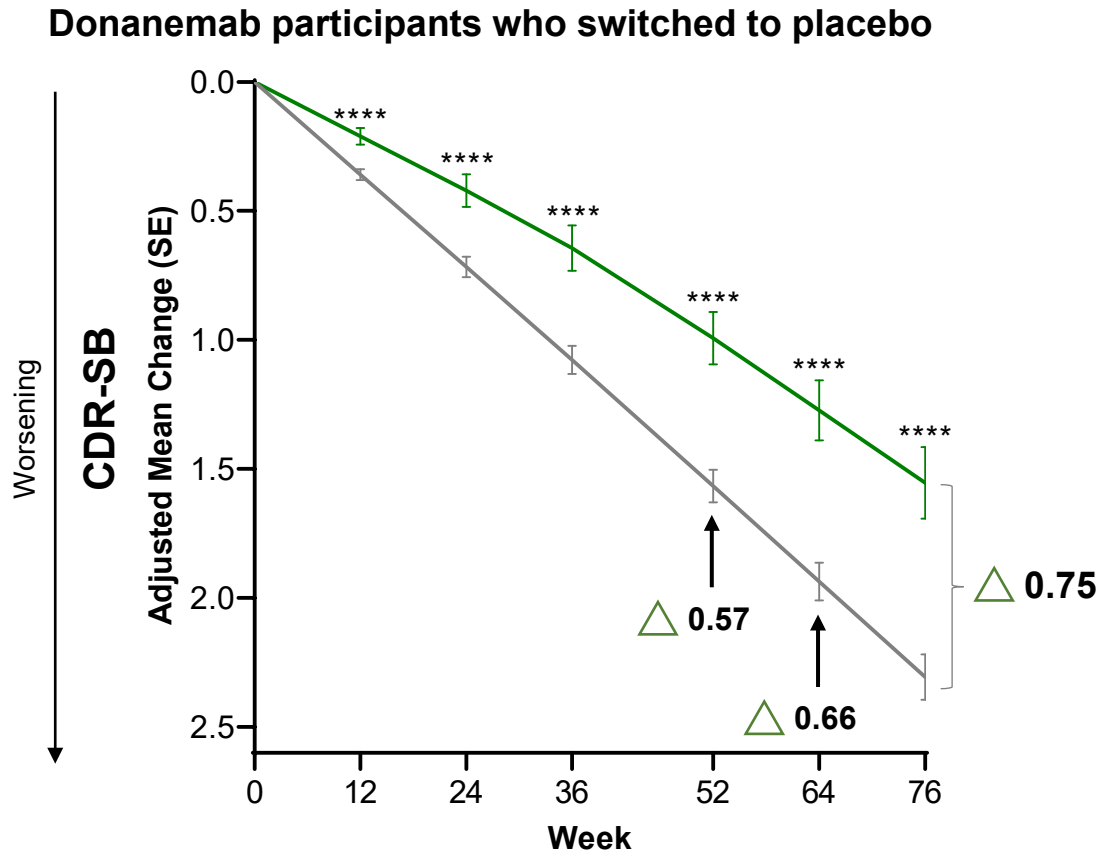
Mean time in trial prior to switch to placebo for these participants: 47 weeks

iADRS: Combined Tau Population



Placebo	797	779	761	738	693	651	653
Donanemab	296	290	288	285	282	266	268

CDR-SB: Combined Tau Population



Placebo	810	798	778	752	713	678	672
Donanemab	301	297	294	292	290	275	275

iADRS and CDR-SB used the NCS model with 2 degrees of freedom adjusted for basis expansion terms (two terms), basis expansion term-by-treatment interaction, and covariates for age at baseline, pooled investigator, baseline tau level, and baseline acetylcholinesterase inhibitor/memantine use. Participants that did not stop treatment were also included in the model but are not plotted here. Nominal P-values: ** P<0.01, *** P<0.001, **** P<0.0001. Abbreviations: CDR-SB=Clinical Dementia Rating–Sum of Boxes; iADRS=Integrated Alzheimer's Disease Rating Scale; NCS=natural cubic spline; SE=Standard Error

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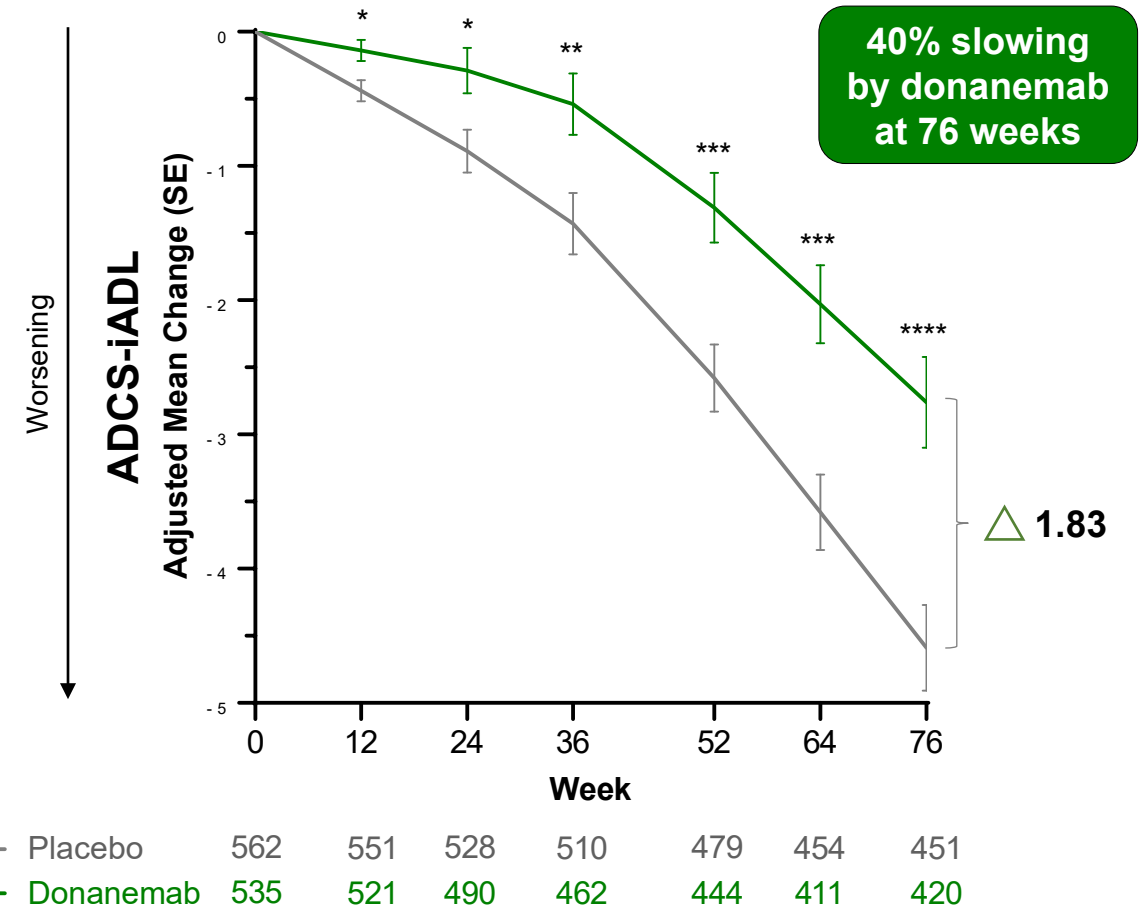
Secondary outcomes: ADCS-iADL and ADAS-Cog$_{13}$

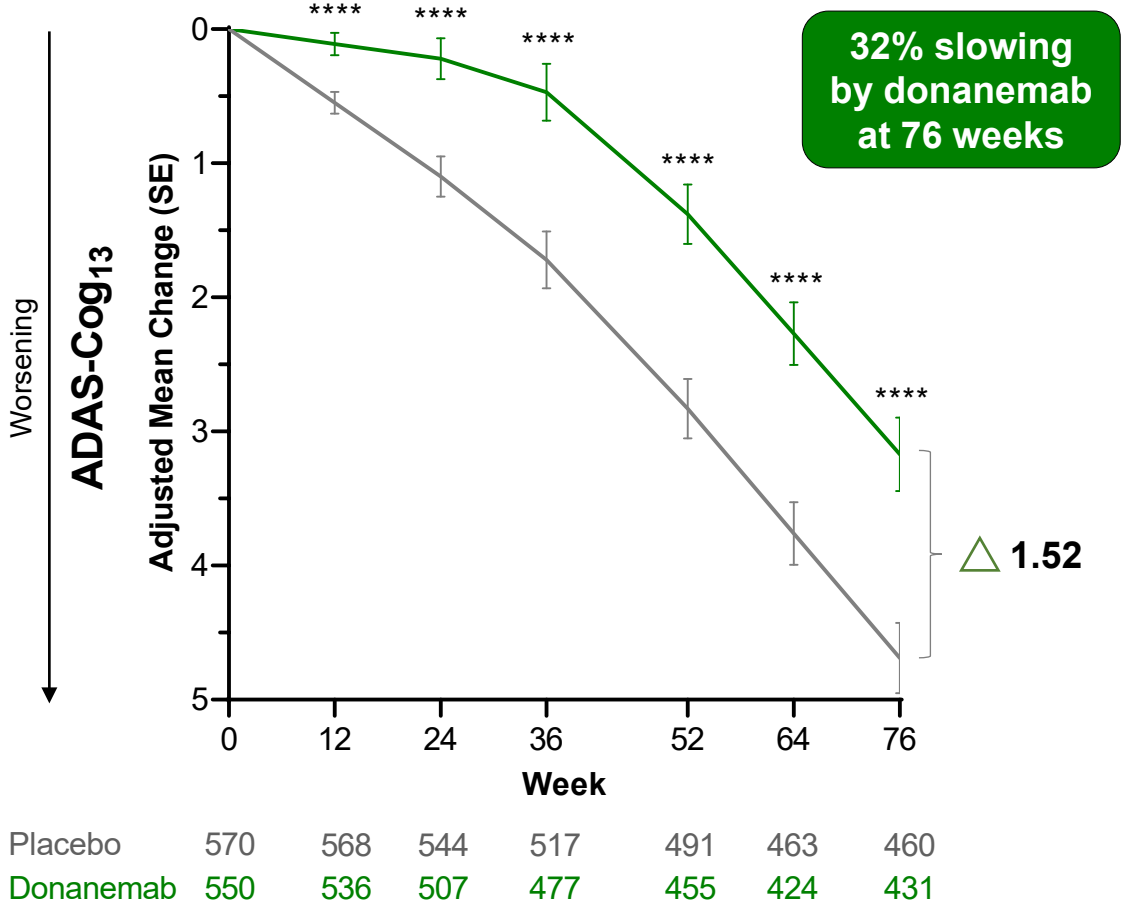
Efficacy in both Function and Cognition Subscales of iADRS

ADCS-iADL: Low-medium Tau Population



Placebo	562	551	528	510	479	454	451
Donanemab	535	521	490	462	444	411	420

ADAS-Cog$_{13}$: Low-medium Tau Population



Placebo	570	568	544	517	491	463	460
Donanemab	550	536	507	477	455	424	431

Both analyses used the NCS model with 2 degrees of freedom adjusted for basis expansion terms (two terms), basis expansion term-by-treatment interaction, and covariates for age at baseline, pooled investigator, and baseline acetylcholinesterase inhibitor/memantine use. * P<0.05, ** P<0.01, *** P<0.001, **** P<0.0001. Abbreviations: ADCS-iADL=Alzheimer's Disease Cooperative Study–instrumental Activities of Daily Living Inventory; ADAS-Cog$_{13}$=13-item cognitive subscale of the Alzheimer 's Disease Assessment Scale; iADRS= Integrated Alzheimer's Disease Rating Scale; NCS=natural cubic spline; SE=Standard Error

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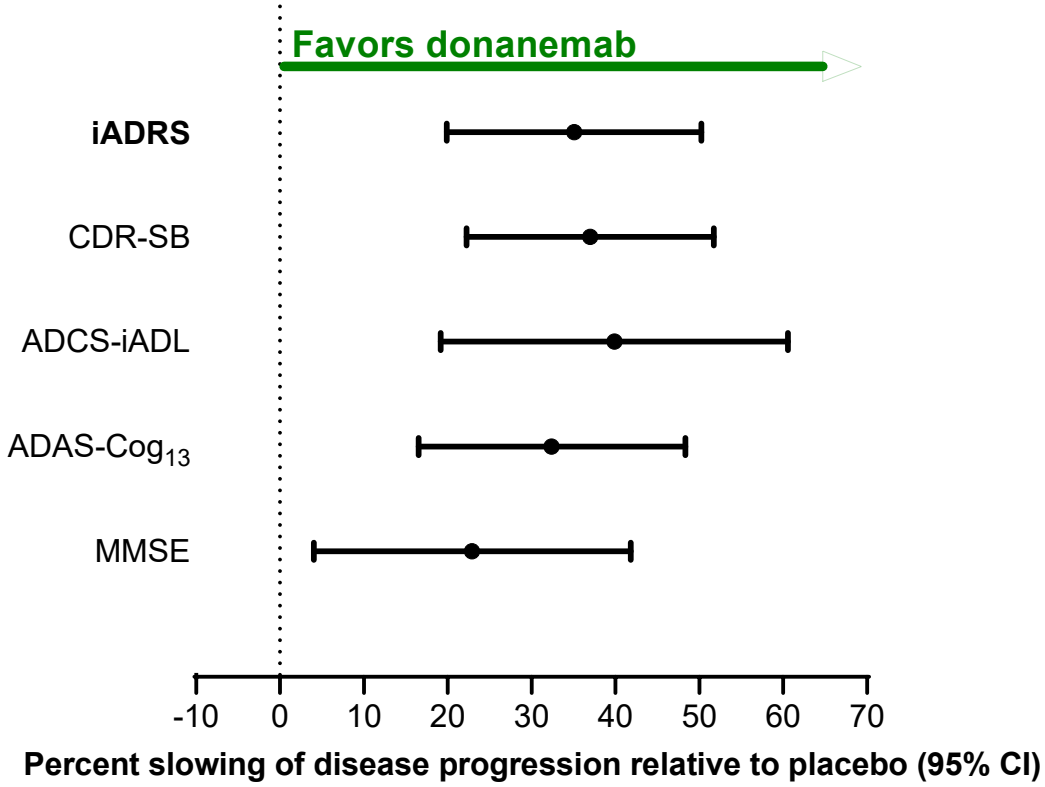
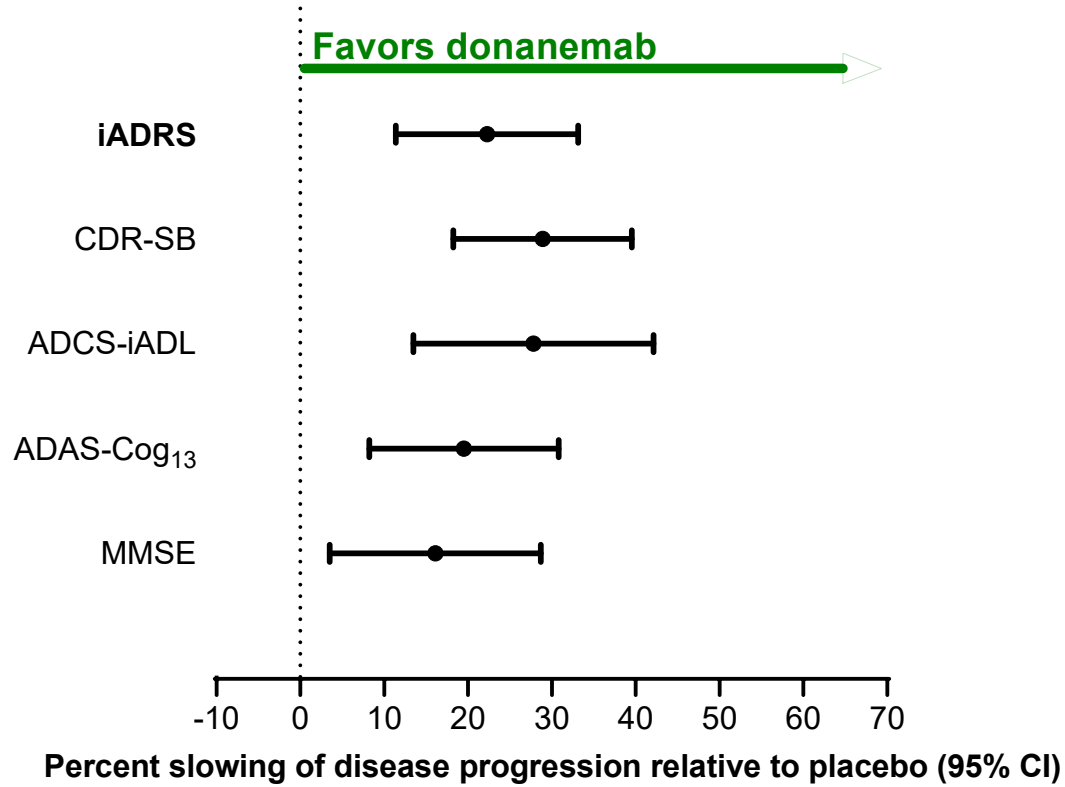
Consistent Effect by Donanemab in Slowing of Disease Progression Across Clinical Scales

Low-medium Tau Population



Combined Tau Population



NCS model with 2 degrees of freedom (used for all scales except CDR-SB) adjusted for basis expansion terms (two terms), basis expansion term-by-treatment interaction, and covariates for age at baseline, pooled investigator, baseline tau level (overall model only), and baseline acetylcholinesterase inhibitor/memantine use. For CDR-SB: adjusted mean change from baseline, SE, 95% CI and p-value are derived using mixed model repeated measures methodology with fixed factors for treatment, visit, treatment-by-visit interaction, and covariates for baseline score, baseline score-by-visit interaction, age at baseline, pooled investigator, baseline acetylcholinesterase inhibitor/memantine use and baseline tau category (combined population only). 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–Sum of Boxes; iADRS=Integrated Alzheimer's Disease Rating Scale; MMSE=Mini–Mental State Examination; NCS=natural cubic spline; SE=standard error

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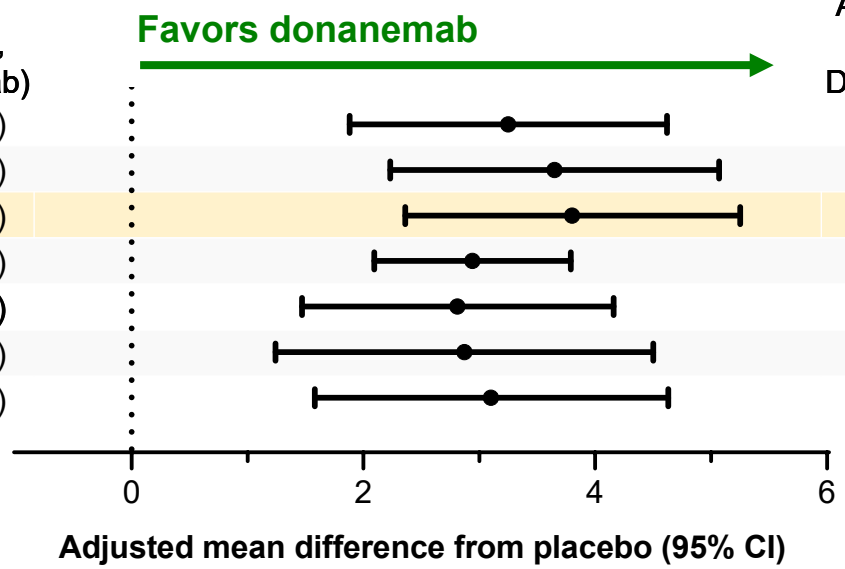
Sensitivity Analyses:
Consistent findings by multiple statistical methods & censoring after ARIA-E/IRRs

iADRS: Low-medium Tau Population

	Baseline N's (Placebo, Donanemab)	Week 76 N's (Placebo, Donanemab)	Adjusted Mean Difference	Percent Slowing
Natural Cubic Spline Model with 2 degrees of freedom (NCS2)	(560,533)	(444,418)	3.3	35.1
Natural Cubic Spline Model with 3 degrees of freedom	(560,533)	(444,418)	3.7	39.1
Mixed Model Repeated Measures	(560,533)	(444,418)	3.8	39.6
Disease Progression Model	(560,533)	(444,418)	2.9	34.0
NCS2 in completers population	**(465,421)**	**(443,416)**	**2.8**	**34.5**
NCS2 in per protocol population	(275,268)	(275,268)	2.9	35.0
NCS2 censored post ARIA-E/IRR	(559,533)	(435,299)	3.1	33.4



Sensitivity analyses of treatment difference and percent slowing at 76 weeks in the donanemab group as compared with placebo group. The efficacy evaluable population (all randomized participants with a baseline and at least one post-baseline efficacy scale) was assessed unless noted. Completers are all randomized participants who completed the placebo-controlled, double-blinded phase and the per protocol population is 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 95% CIs (except for DPM which shows credible intervals over the entire 18-month intervention period). CIs were not adjusted for multiple comparisons, and no definite conclusions can be drawn. Abbreviations: ARIA-E=amyloid-related imaging abnormalities-edema/effusion; iADRS=Integrated Alzheimer's Disease Rating Scale; CI=confidence interval; DPM=Disease Progression Model; IRR=infusion-related reactions; N=number of participants; NCS=natural cubic spline

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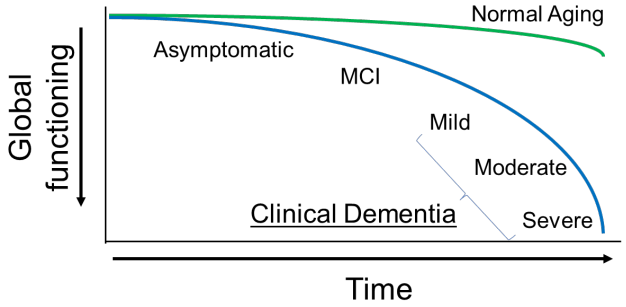
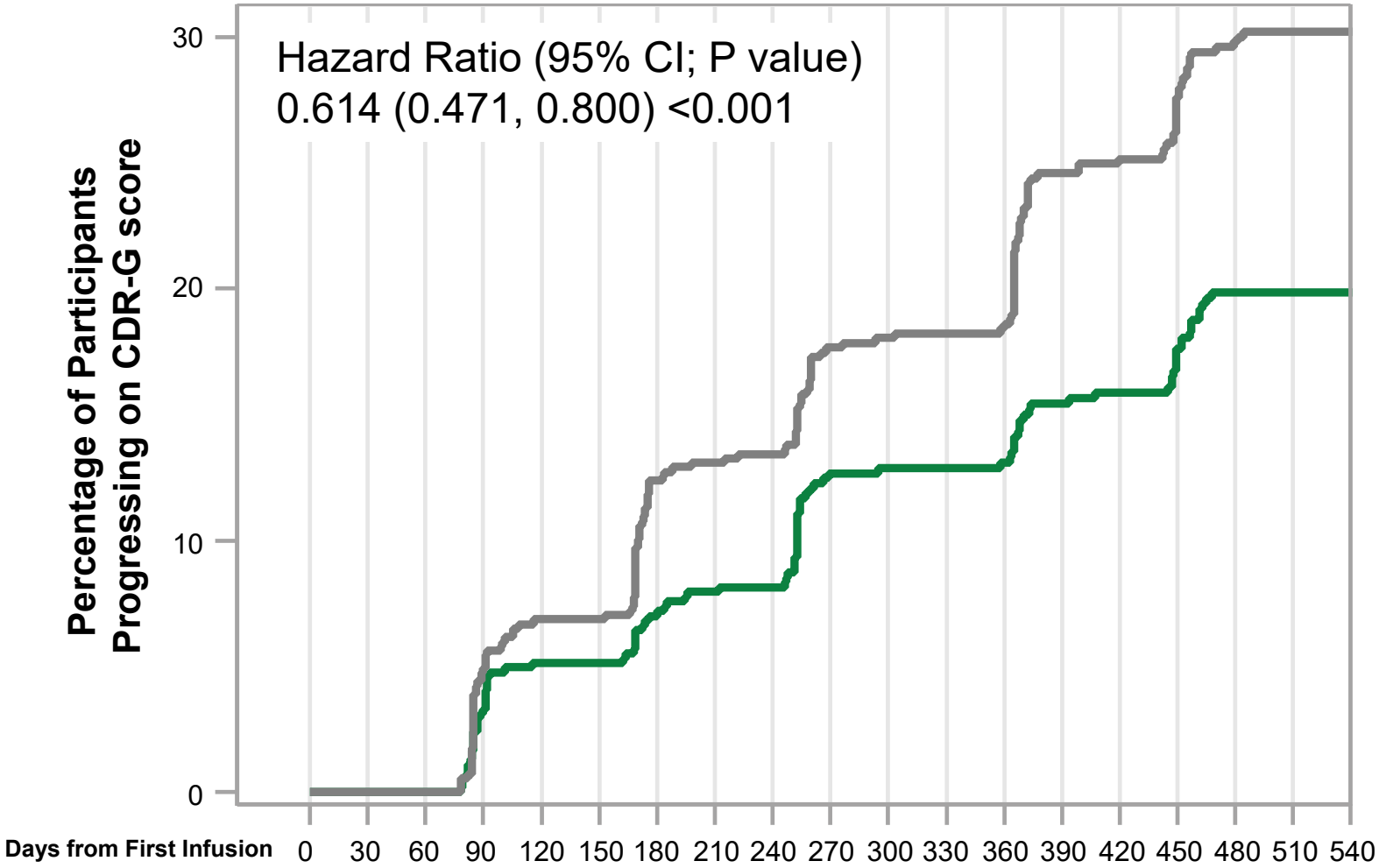
Risk of Progression: CDR-Global score

Low-medium Tau population



Modified from Sperling, A (2011). Alzheimer's & Dementia, 7, 280–292. https://doi.org/10.1016/j.jalz.2011.03.003



38.6% lower risk of progression over 76 weeks

	Placebo	Donanemab
N	573	555
Event	163	100
Time	% (SE) n at risk	% (SE) n at risk
60 days	0.0 (0.00) 570	0.0 (0.00) 552
120 days	6.8 (1.06) 529	5.1 (0.94) 514
180 days	12.4 (1.38) 489	7.2 (1.11) 492
240 days	13.4 (1.44) 474	8.1 (1.18) 470
360 days	18.6 (1.65) 425	13.1 (1.47) 412
480 days	29.8 (1.98) 345	19.9 (1.79) 335

Definition of event: an increase from baseline in CDR-G score at two consecutive visits. Hazard ratio and P-value were generated using a Cox proportional hazards model adjusted for baseline age, baseline value, and baseline acetylcholinesterase inhibitor/memantine use and stratified by pooled investigator. Abbreviations: CDR-G=Clinical Dementia Rating-Global Scale; CI=confidence interval; MCI=mild cognitive impairment; N=number of participants; SE=standard error

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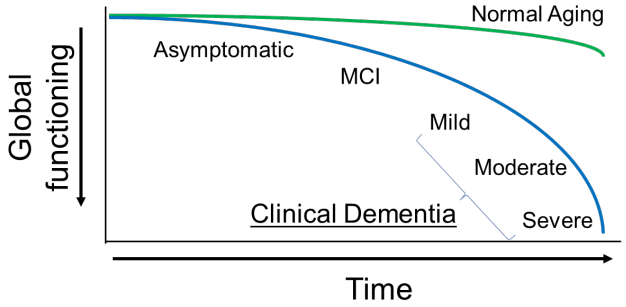
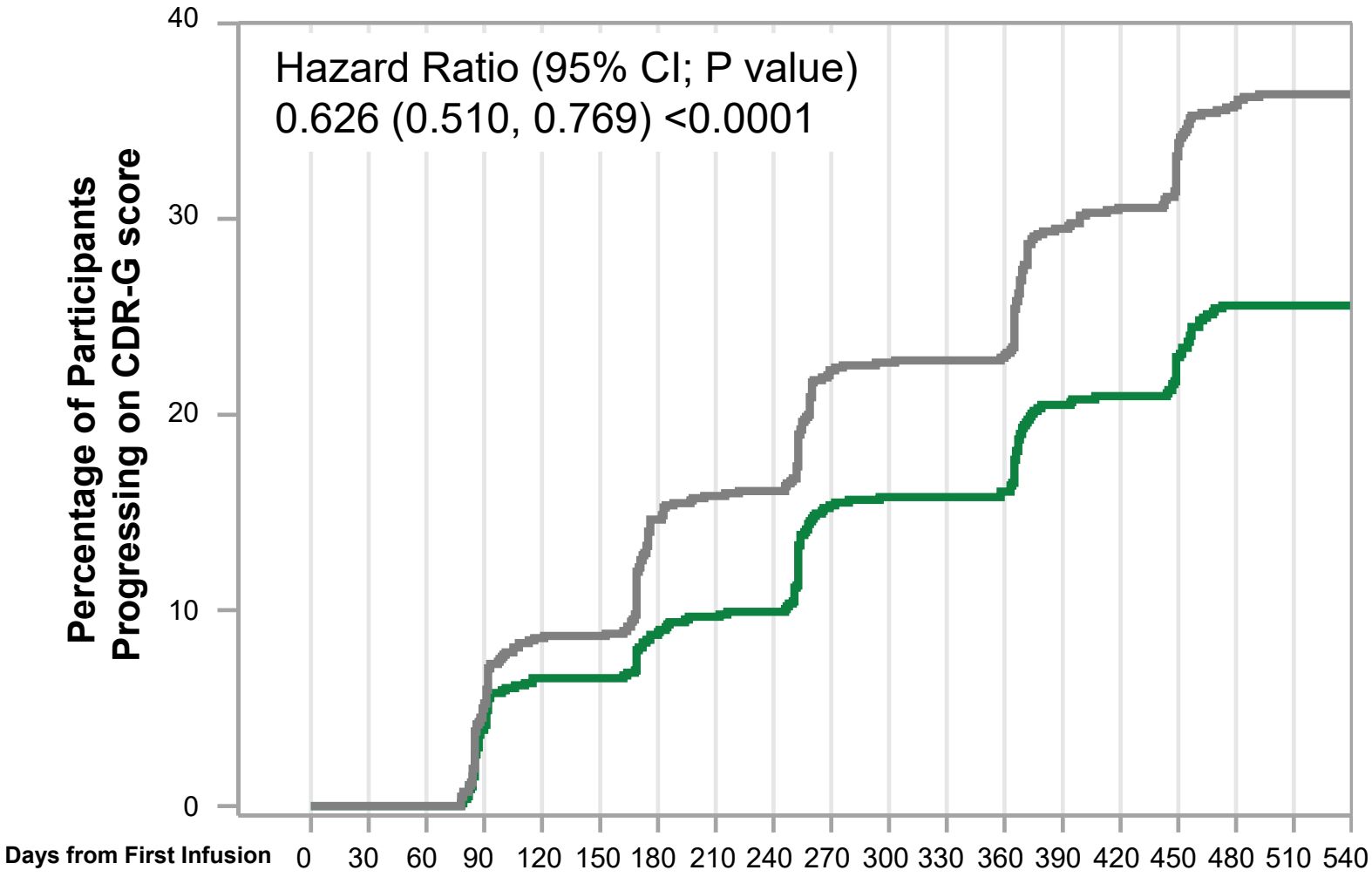
Risk of Progression: CDR-Global score
Combined Tau population



Modified from Sperling, A (2011). Alzheimer's & Dementia, 7, 280–292. https://doi.org/10.1016/j.jalz.2011.03.003



37.4% lower risk of progression over 76 weeks

	Placebo	Donanemab
N	844	805
Event	288	186
Time	% (SE) n at risk	% (SE) n at risk
60 days	0.0 (0.00) 840	0.0 (0.00) 801
120 days	8.6 (0.97) 764	6.5 (0.88) 737
180 days	14.6 (1.22) 700	8.9 (1.01) 696
240 days	16.1 (1.27) 671	9.9 (1.07) 668
360 days	23.0 (1.47) 587	16.1 (1.33) 575
480 days	35.8 (1.72) 462	25.6 (1.63) 474

Definition of event: an increase from baseline in CDR-G score at two consecutive visits. Hazard ratio and P-value were generated using a Cox proportional hazards model adjusted for baseline age, baseline value, and baseline acetylcholinesterase inhibitor/memantine use and stratified by pooled investigator and baseline tau level. Abbreviations: CDR-G=Clinical Dementia Rating-Global Scale; CI=confidence interval; MCI=mild cognitive impairment; N=number of participants; SE=standard error

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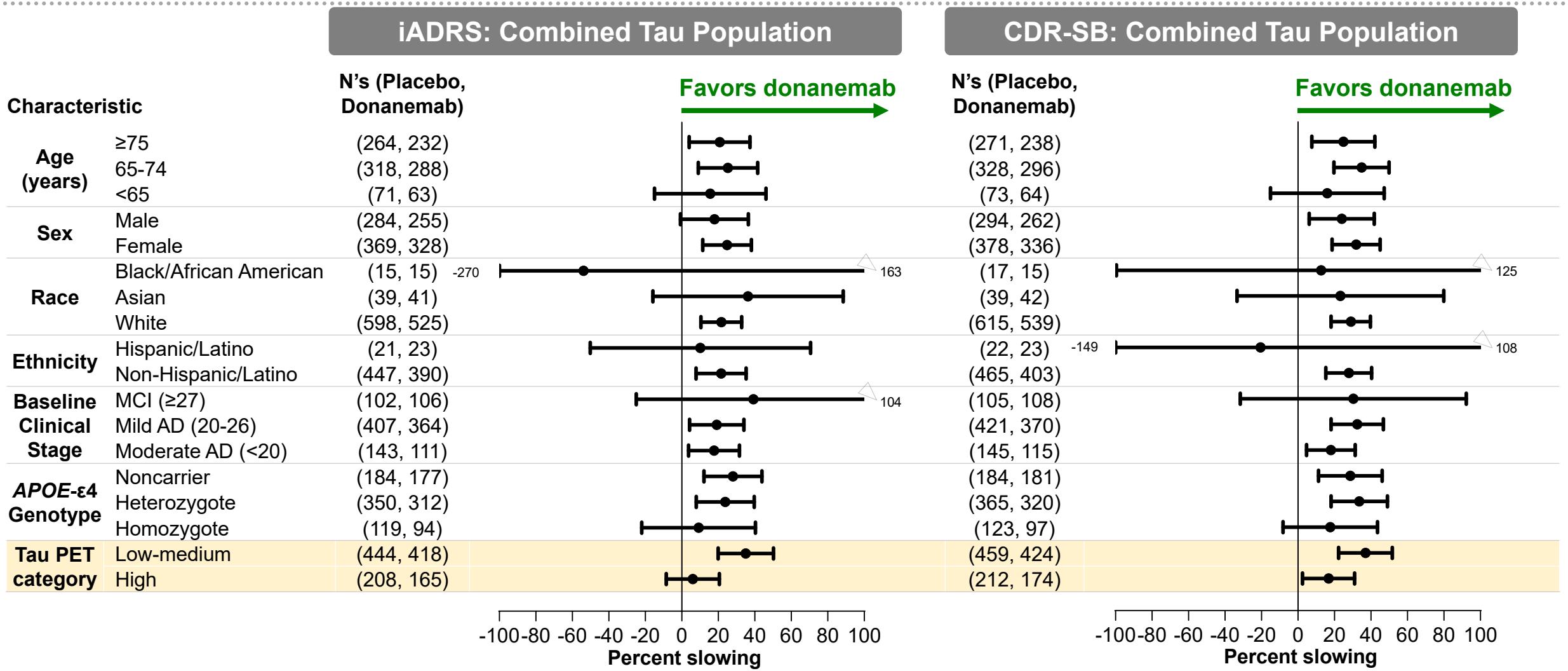
Subgroup Analyses:
Combined Tau Population



NCS model with 2 degrees of freedom adjusted for basis expansion terms (two terms), basis expansion term-by-treatment interaction, and covariates for age at baseline, pooled investigator, baseline tau level and baseline acetylcholinesterase inhibitor/memantine use. Additional fixed terms include subgroup by treatment, subgroup by basis expansion, and subgroup by basis expansion by treatment interactions. Bars show the 95% confidence intervals; values are included for those that extend past the limits of the axis.

Abbreviations: AD=Alzheimer's Disease; APOE=apolipoprotein E; CDR-SB=Clinical Dementia Rating Scale–Sum of Boxes; iADRS=Integrated Alzheimer's Disease Rating Scale; MCI=mild cognitive impairment; N=number of participants; NCS=natural cubic spline; PET=positron emission tomography

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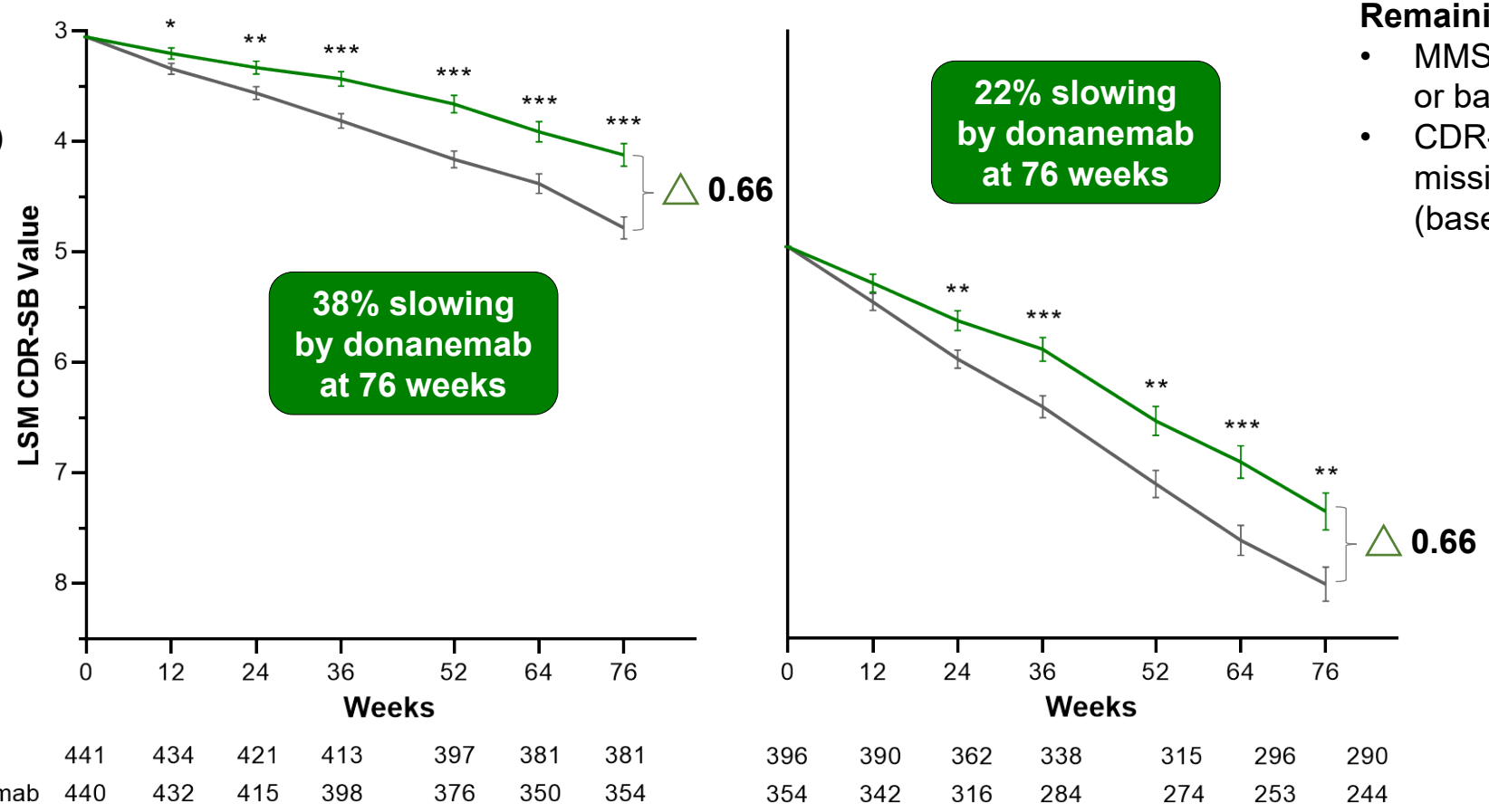
Key Secondary Outcome: CDR-SB

Population Selected by Clinical Screening Criteria used in other Contemporary Trials

Typical Population based on:

- MMSE of 22-30 (at screening and baseline)
- CDR-G Score ≤1 (baseline)



Remaining Population:

- MMSE <22 (at screening or baseline)
- CDR-G Score >1 or missing CDR-G Score (baseline)

Donanemab demonstrates efficacy in participants typically excluded based on initial clinical scale scores

CDR-SB: adjusted mean change from baseline, SE, and p-value are derived using mixed model repeated measures methodology with fixed factors for treatment, visit, treatment-by-visit interaction, and covariates for baseline score, baseline score-by-visit interaction, age at baseline, baseline acetylcholinesterase inhibitor/memantine use and baseline tau category. The plotted values account for the different baseline means between the subpopulations. Nominal P-values: * P<0.05, ** P<0.01, *** P<0.001, Abbreviations: CDR-SB=Clinical Dementia Rating–Sum of Boxes; CDR-G=Clinical Dementia Rating-Global Scale; LSM=least squares mean; MMSE=Mini–Mental State Examination; SE=Standard Error

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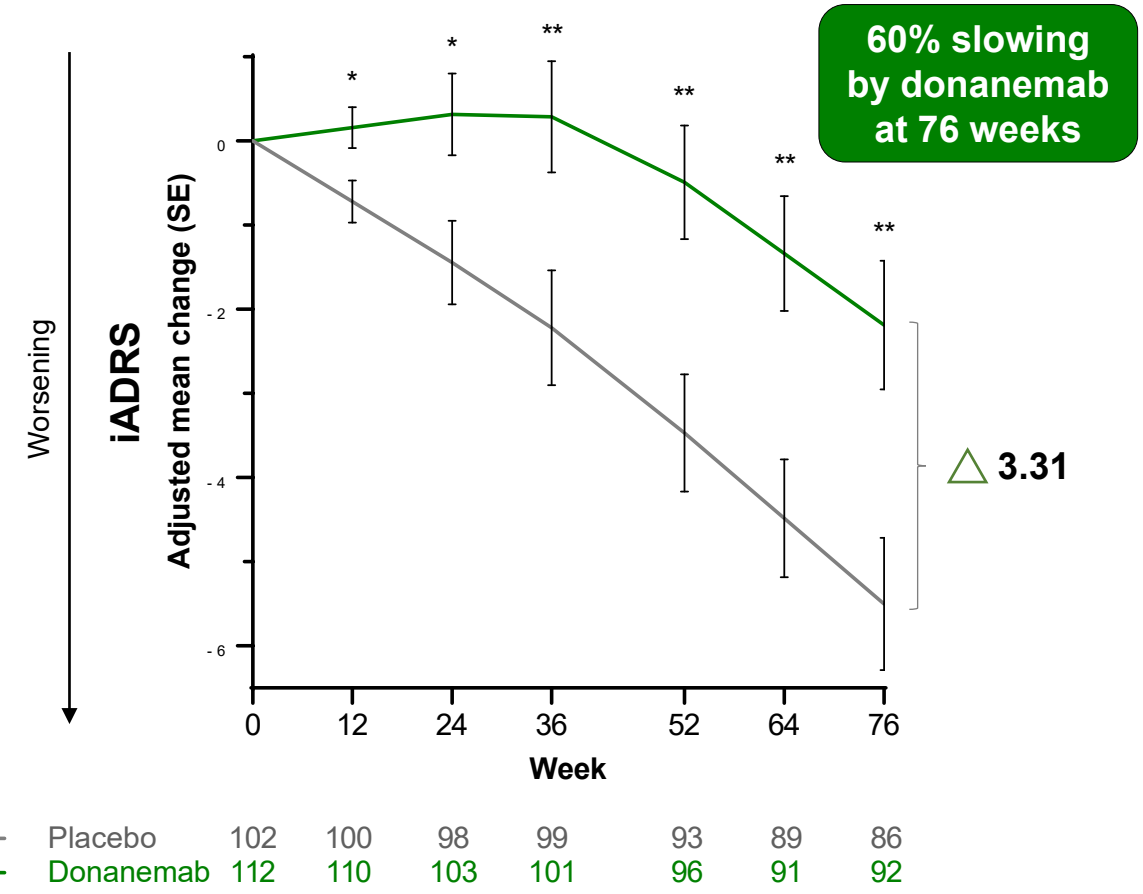
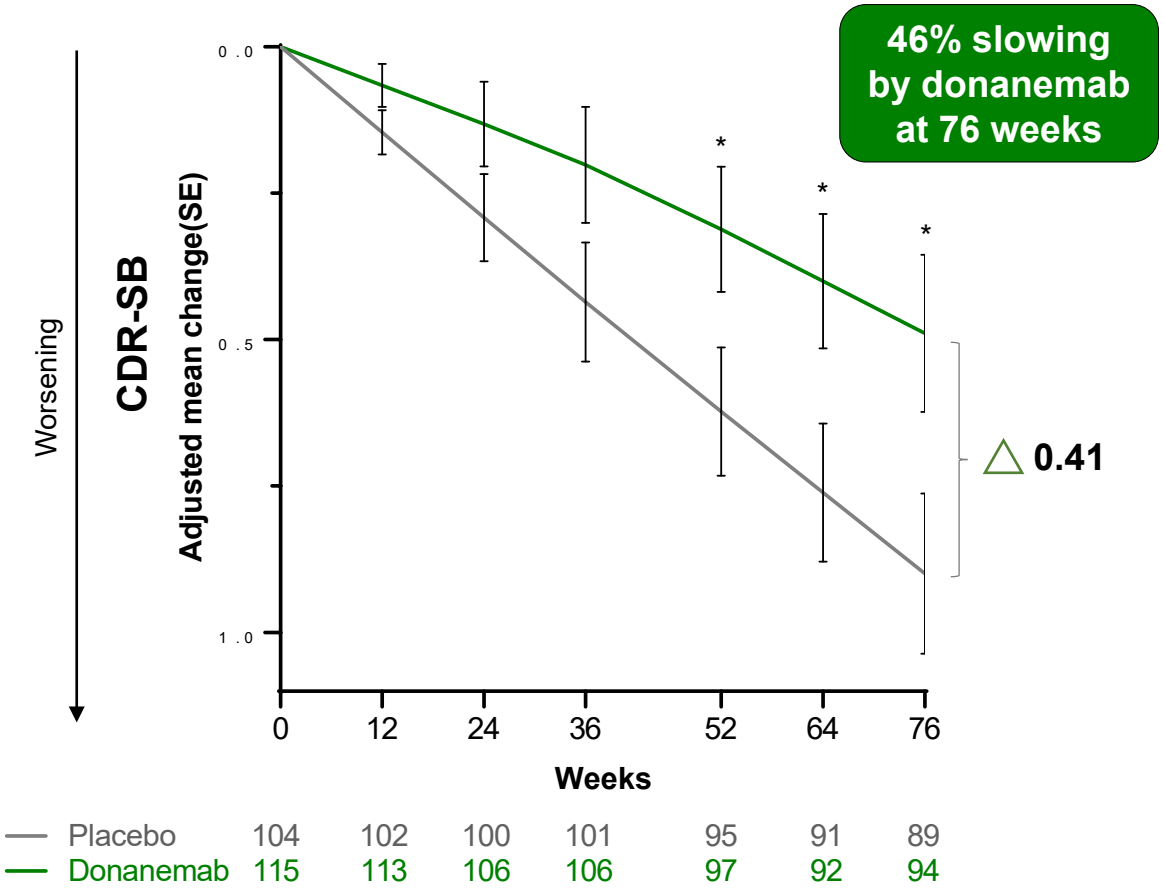
Pre-specified Subpopulation: MCI
Low-medium Tau Population

iADRS



CDR-SB



Donanemab showed greater clinical impact in participants at earlier disease stage

MCI=MMSE ≥27 at baseline. SE, 95% CI and p-value are derived using NCS model with 2 degree of freedom. The model was adjusted for basis expansion terms (two terms), basis expansion term-by-treatment interaction and covariates for age at baseline, pooled investigator, and baseline acetylcholinesterase inhibitor/memantine use. Nominal P-values: * P<0.05, ** P<0.01. Abbreviations: CDR-SB=Clinical Dementia Rating–Sum of Boxes; CI=confidence interval; iADRS=Integrated Alzheimer's Disease Rating Scale; MCI=mild cognitive impairment; MMSE=Mini–Mental State Examination; NCS=natural cubic spline; SE=Standard Error

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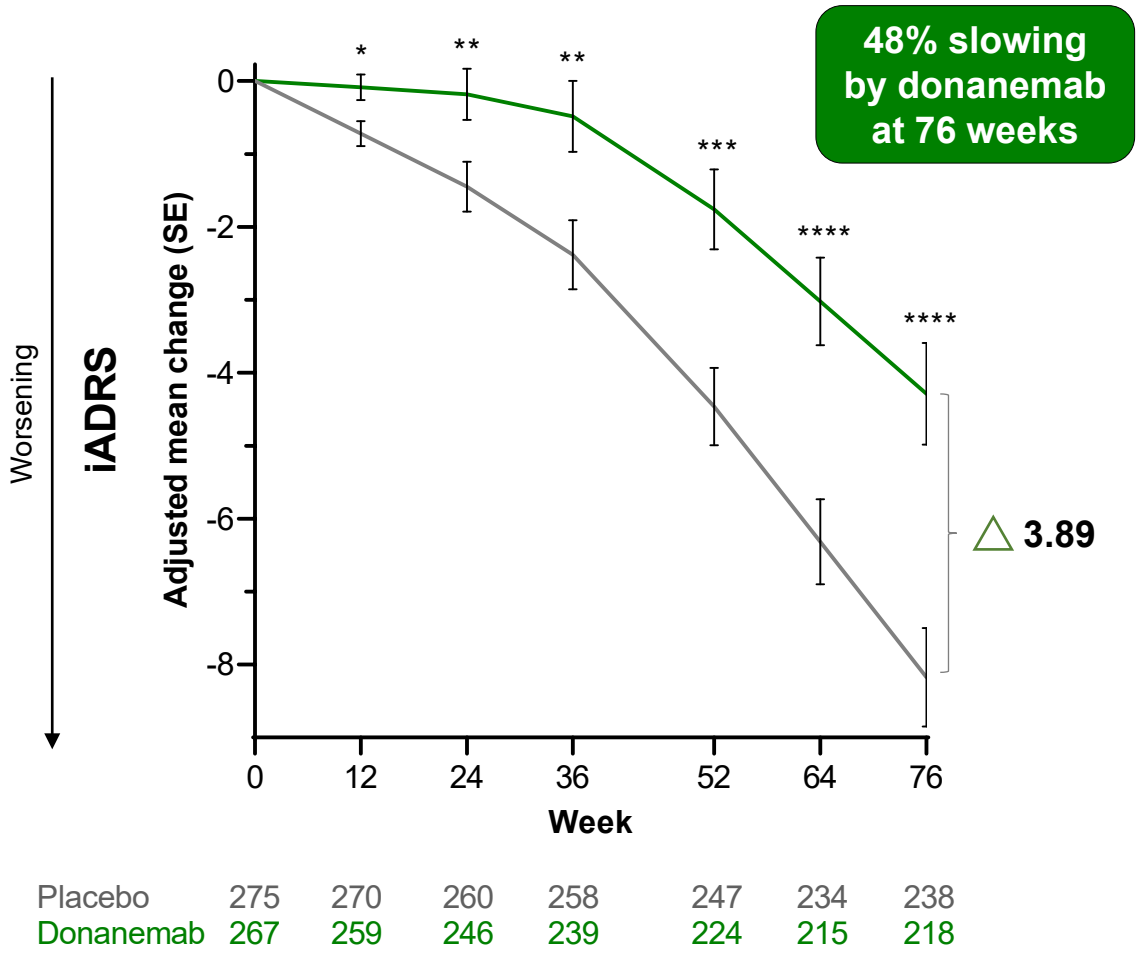
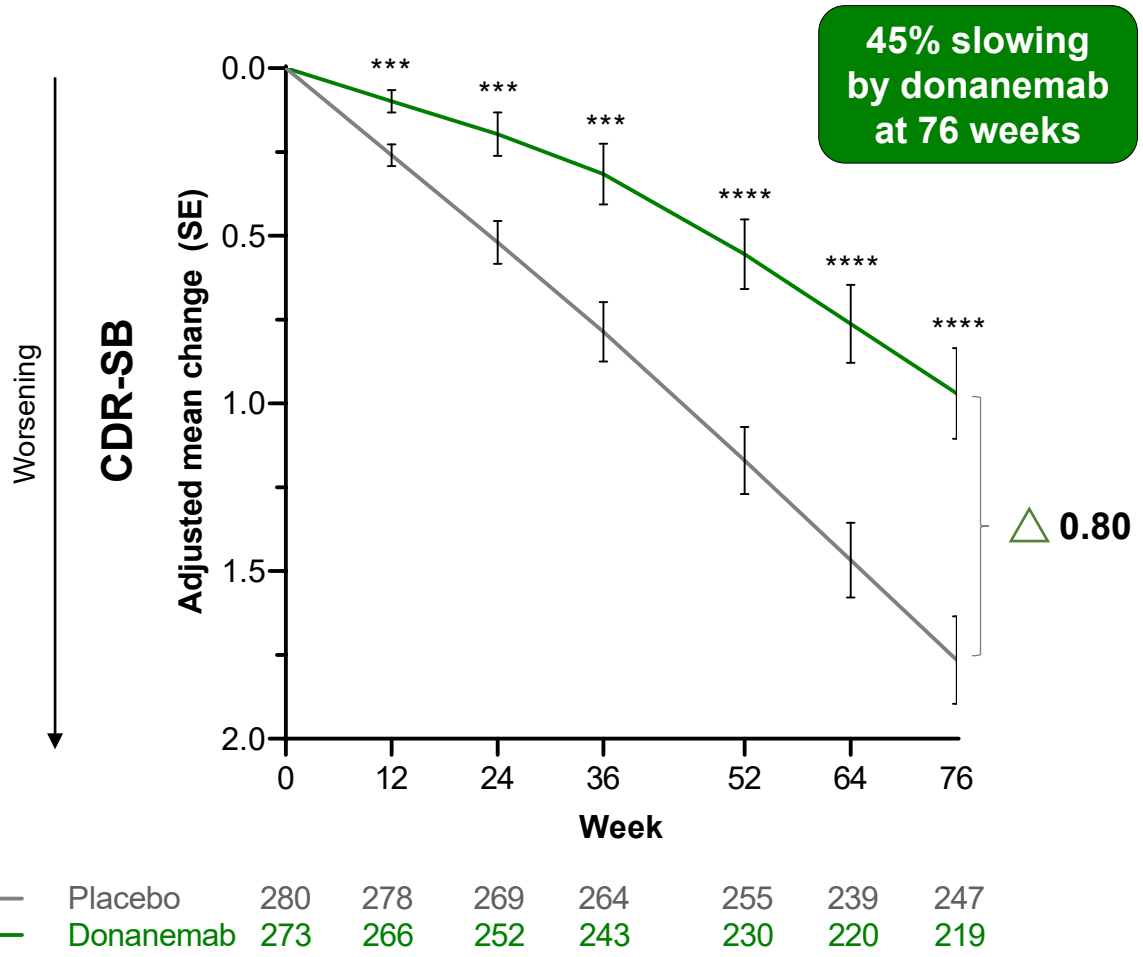
Subgroup: Younger Participants
Low-medium Tau Population

iADRS: Age <75 years



Placebo	275	270	260	258	247	234	238
Donanemab	267	259	246	239	224	215	218

CDR-SB: Age <75 years



Placebo	280	278	269	264	255	239	247
Donanemab	273	266	252	243	230	220	219

NCS model with 2 degrees of freedom adjusted for basis expansion terms (two terms), basis expansion term-by-treatment interaction, and covariates for age at baseline, pooled investigator, baseline tau level and baseline acetylcholinesterase inhibitor/memantine use. Additional fixed terms include subgroup by treatment, subgroup by basis expansion, and subgroup by basis expansion by treatment interactions. Nominal P-values: * P<0.05, ** P<0.01, *** P<0.001, **** P<0.0001. Abbreviations: iADRS=Integrated Alzheimer's Disease Rating Scale; NCS=natural cubic spline; SE=standard error

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Summary

- TRAILBLAZER-ALZ 2 demonstrated that donanemab significantly slowed cognitive and functional decline in early symptomatic Alzheimer's disease, providing an important replication of the successful Phase 2 study
- Importantly, efficacy extends into the broader combined study population
- Consistency across all gated cognitive and functional secondary endpoints, and across multiple analysis methods
- Participants completing treatment regimen continue to separate from placebo
- First data generated to test the hypothesis that pathology can inform response to treatment and progression
- Treating earlier in symptomatic disease is supported by tau pathology analyses, clinical stage and age analyses
- Data support and hold promise for studies in preclinical stage of the disease

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Donanemab in Early Symptomatic Alzheimer's Disease: Safety Results from TRAILBLAZER-ALZ 2

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Alzheimer's Association International Conference (AAIC)
Amsterdam, Netherlands, and Online
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Disclosures

- Research support: Avid, Biogen, Eisai, Eli Lilly and Company, Genentech, Roche
- Consulting: Acumen, Amylyx, Biogen, Bolden, Eisai, Eli Lilly and Company, Genentech, Novo Nordisk, Prothena, Roche
- Site PI for trials of aducanumab, donanemab, lecanemab, and gantenerumab, Project Arm Leader for gantenerumab in DIAN-TU, co-author for the Appropriate Use Recommendations for aducanumab and lecanemab

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Safety overview

Objective: To evaluate safety and tolerability of donanemab

- Safety analyses presented here are from the combined population (low/medium/high tau) in the double-blind period of TRAILBLAZER-ALZ 2
- Unblinded safety data reviews were performed quarterly by an external Data Monitoring Committee
- Endpoints:
  - Standard safety assessments
    - Spontaneously reported AEs
    - Clinical laboratory tests
    - Vital sign and body weight measurements
    - 12-lead ECGs
    - Physical and neurological examinations
  - Columbia Suicide Severity Rating Scale
  - Infusion-related reactions
  - MRIs completed at screening, 4,12, 24, 52, 76 weeks, unscheduled at investigator's discretion, and every 4-6 weeks until resolution of ARIA-E and stabilization of ARIA-H
    - Participants were excluded from trial if screening MRI showed >4 cerebral microhemorrhages, >1 area of superficial siderosis, macrohemorrhage, severe white matter disease or ARIA-E

Abbreviations: AE=adverse event; ARIA-E=amyloid-related imaging abnormalities-edema/effusions; ARIA-H=amyloid-related imaging abnormalities-microhemorrhages/hemosiderin deposits; ECG=electrocardiogram; MRI=magnetic resonance imaging

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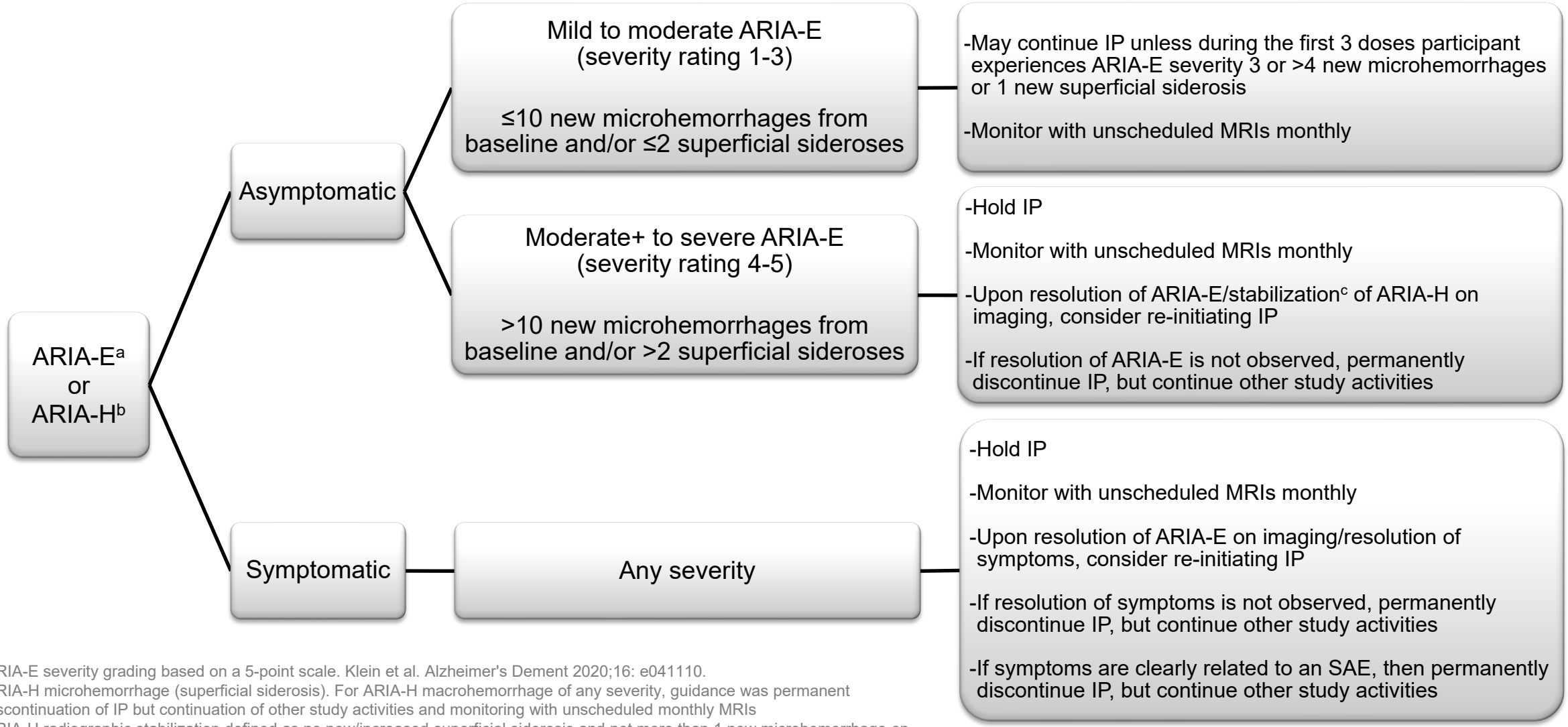
ARIA management guidance



[a] ARIA-E severity grading based on a 5-point scale. Klein et al. Alzheimer's Dement 2020;16: e041110.
[b] ARIA-H microhemorrhage (superficial siderosis). For ARIA-H macrohemorrhage of any severity, guidance was permanent discontinuation of IP but continuation of other study activities and monitoring with unscheduled monthly MRIs
[c] ARIA-H radiographic stabilization defined as no new/increased superficial siderosis and not more than 1 new microhemorrhage on subsequent MRI

Abbreviations: ARIA-E=amyloid-related imaging abnormalities-edema/effusions; ARIA-H=amyloid-related imaging abnormalities-microhemorrhages/hemosiderin deposits; IP=investigational product; MRI=magnetic resonance imaging; SAE=serious adverse event

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Safety overview - combined population

Summary of Adverse Events

Participants[a], n (%)	Placebo (N=874)	Donanemab (N=853)
Death[b]	10 (1.1)	16 (1.9)
Death considered related to treatment	1 (0.1)	3 (0.4)
Serious AE	138 (15.8)	148 (17.4)
Study discontinuations due to AE	32 (3.7)	69 (8.1)
Treatment discontinuations due to AE	38 (4.3)	112 (13.1)
Treatment-emergent AEs	718 (82.2)	759 (89.0)
Treatment-emergent AEs deemed related to study treatment[c]	173 (19.8)	410 (48.1)

[a] Participants may be counted in more than one category.
[b] Deaths are also included as serious AEs and discontinuations due to AEs.
[c] Includes events that were considered related to study treatment as judged by the investigator.
Treatment-emergent adverse event is defined as an event that first occurred or worsened after the treatment initiation date and up to either the first visit date of long-term extension phase - 1 day or end of treatment period in double-blinded phase + 57 days, whichever occurs first.

- Treatment discontinuation due to adverse events occurred more frequently in the donanemab group, including:
  - IRR (3.6%)
  - ARIA-E (2.5%)
  - ARIA-H (0.8%)
  - Hypersensitivity (0.5%)

Abbreviations: AE=adverse event; ARIA-E=amyloid-related imaging abnormalities-edema/effusions; ARIA-H=amyloid-related imaging abnormalities-hemorrhage/hemosiderin deposition; IRR=infusion-related reaction; N, n=number of participants

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Adverse events leading to death

Preferred term, n	Placebo	Donanemab
ARIA-E[a]	0	1
ARIA-H[a]	0	1
Arteriosclerosis[a]	1	0
Death[b,c]	1	3
Completed suicide	1	2
COVID-19 related	0	2
Dehydration	0	1
Dementia Alzheimer's type	1	1
Myocardial infarction	1	0
Pulmonary embolism	0	2
Pneumonia	2	0
Respiratory arrest	0	1
Respiratory failure	1	0
Respiratory fume inhalation disorder	1	0
Retroperitoneal hemorrhage	0	1
Sepsis	1	0
Subarachnoid hemorrhage[d]	0	1
Total	**10**	**16**

- 3 participants in the donanemab group with serious ARIA subsequently died
  - None were prescribed anti-coagulants or anti-platelet medications
  - Two developed severe ARIA-E, one following re-treatment after resolution of severe ARIA-E and stabilization of severe ARIA-H
  - One had superficial siderosis at baseline and later developed a large intracerebral hemorrhage

[a] PI considered related to treatment
[b] One case in donanemab arm considered related to treatment and with SAEs of ARIA-E and ARIA-H
[c] Cause not specified or unknown
[d] Occurred while on placebo infusions

Abbreviations: ARIA-E=amyloid-related imaging abnormalities-edema/effusions; ARIA-H=amyloid-related imaging abnormalities-hemorrhage/hemosiderin deposition; n=number of participants; PI=principal investigator; SAE=serious adverse event

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Treatment-emergent adverse events

Treatment-Emergent AE ≥5%[#]		
Preferred Term, n (%)	**Placebo** (N=874)	**Donanemab** (N=853)
Participants with ≥1 TEAE	718 (82.2)	759 (89.0)
ARIA-E	**17 (1.9)**	**205 (24.0)**
ARIA-H	**65 (7.4)**	**168 (19.7)**
COVID-19	154 (17.6)	136 (15.9)
Headache	**86 (9.8)**	**119 (14.0)**
Fall	110 (12.6)	114 (13.4)
Infusion-related reaction	**4 (0.5)**	**74 (8.7)**
Superficial siderosis of CNS	**10 (1.1)**	**58 (6.8)**
Dizziness	48 (5.5)	53 (6.2)
Arthralgia	42 (4.8)	49 (5.7)
Urinary tract infection	59 (6.8)	45 (5.3)
Diarrhea	50 (5.7)	43 (5.0)
Fatigue	45 (5.1)	42 (4.9)

[#] in donanemab group after rounding

Abbreviations: AE=adverse event; ARIA-E=amyloid-related imaging abnormalities-edema/effusions; ARIA-H=amyloid-related imaging abnormalities-hemorrhage/hemosiderin deposition; CNS=central nervous system; N, n=number of participants; TEAE=treatment-emergent adverse event

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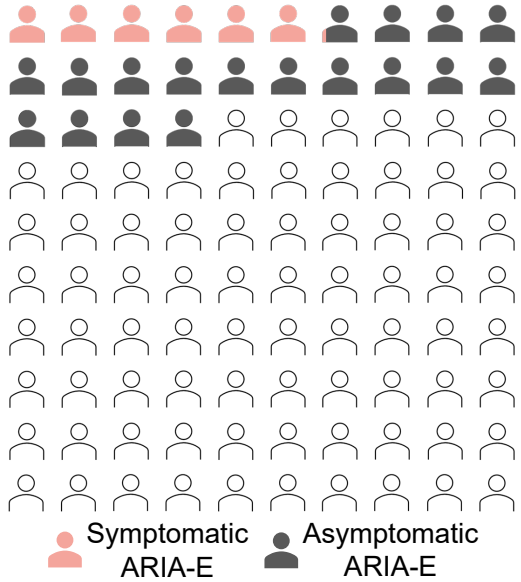
Summary of ARIA and macrohemorrhage

Event[a], n (%)	Placebo (N=874)	Donanemab (N=853)
Any ARIA (-E or -H)	130 (14.9)	314 (36.8)
Any SAE of ARIA	0 (0)	14 (1.6)
ARIA-E	18 (2.1)	205 (24.0)
Asymptomatic	17 (1.9)	153 (17.9)
Symptomatic	1 (0.1)[b]	52 (6.1)
SAE of ARIA-E	0 (0)	13 (1.5)
ARIA-H	119 (13.6)	268 (31.4)
SAE of ARIA-H	0 (0)	4 (0.5)
Isolated ARIA-H	108 (12.4)	108 (12.7)
Macrohemorrhage	2 (0.2)	3 (0.4)
SAE of Macrohemorrhage	1 (0.1)	1 (0.1)

[a] ARIA and macrohemorrhage events based on MRI or TEAE cluster
[b] One placebo-treated participant had ARIA-E during the placebo-controlled period; however, the participant developed symptoms during the long-term extension period

24% of donanemab-treated participants experienced ARIA-E



- ARIA-E events were largely mild to moderate radiographically (94%)
- Commonly reported symptoms of symptomatic ARIA-E were headache and confusion

Abbreviations: ARIA-E=amyloid-related imaging abnormalities-edema/effusions; ARIA-H=amyloid-related imaging abnormalities-hemorrhage/hemosiderin deposition; MRI=magnetic resonance imaging; N, n=number of participants; SAE=serious adverse event; TEAE=treatment-emergent adverse event

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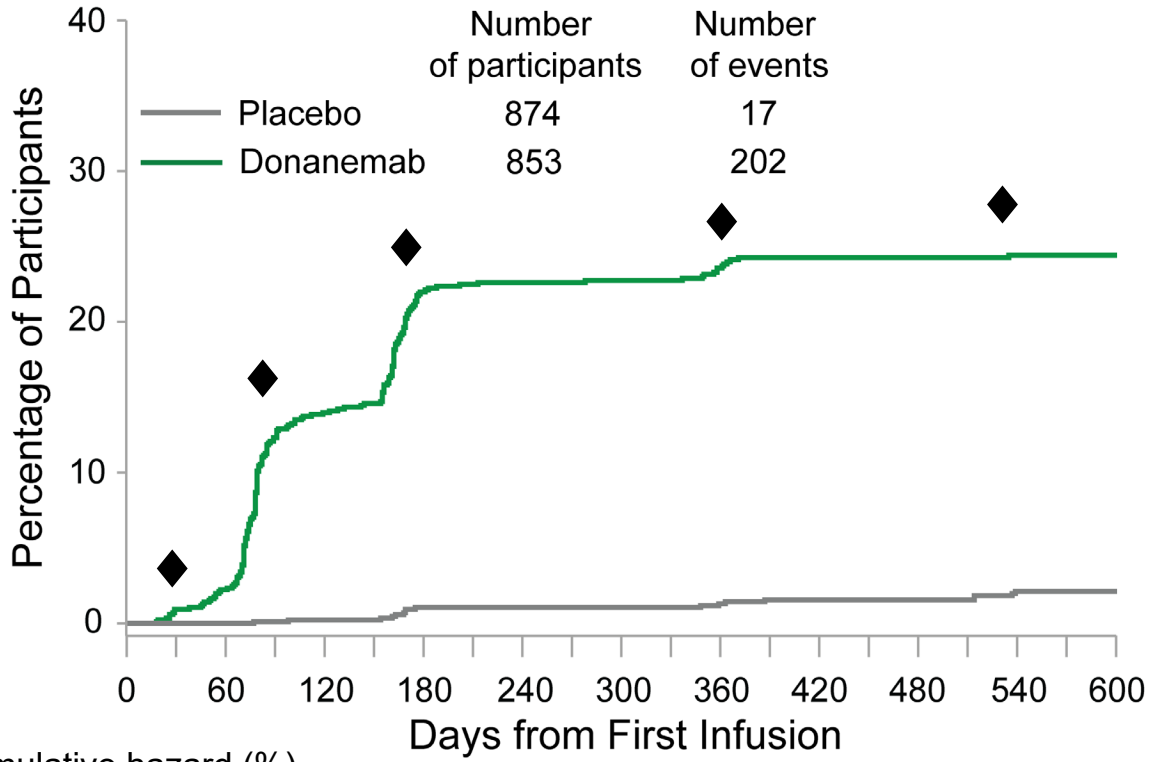
Time to first ARIA-E events

Cumulative hazard of time to first ARIA-E by safety MRI



Cumulative hazard (%)							
Placebo	0.0	0.2	1.1	1.1	1.3	1.6	2.1
Donanemab	2.2	14.0	22.0	22.6	23.6	24.3	24.4

◆ MRIs scheduled at 4, 12, 24, 52, and 76 weeks

- ARIA-E first occurred after receiving up to 3 donanemab infusions in most cases (58%)
- First ARIA-E events radiographically resolved in 98% of participants, with a mean resolution time of around 10 weeks
- 6% of donanemab-treated participants experienced recurrent ARIA-E

Abbreviations: ARIA-E=amyloid-related imaging abnormalities-edema/effusions; MRI=magnetic resonance imaging

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ARIA and *APOE*

ARIA by *APOE* ε4 Carrier Status

No./Total No. (%)[a,b]	Placebo (N=870)	Donanemab (N=850)
ARIA-E		
Non-carrier	2/250 (0.8)	40/255 (15.7)
Heterozygous carrier	9/474 (1.9)	103/452 (22.8)
Homozygous carrier	5/146 (3.4)	58/143 (40.6)
ARIA-H[c]		
Non-carrier	28/250 (11.2)	48/255 (18.8)
Heterozygous carrier	57/474 (12.0)	146/452 (32.3)
Homozygous carrier	30/146 (20.5)	72/143 (50.3)

[a] Based on MRI.
[b] Participants with missing *APOE* ε4 carrier status are excluded.
[c] Treatment-emergent microhemorrhage is based on new incidents of microhemorrhages. Treatment-emergent superficial siderosis is based on new or worsening superficial siderosis.

- Participants with at least 1 serious ARIA event[d]
  - ARIA-E: 12 *APOE* ε4 carriers and 1 non-carrier
  - ARIA-H: 3 *APOE* ε4 carriers and 1 non-carrier

[d] SAEs are by AE reporting

Abbreviations: *APOE*=apolipoprotein E; ARIA-E=amyloid-related imaging abnormalities-edema/effusions; ARIA-H=amyloid-related imaging abnormalities-hemorrhage/hemosiderin deposition; MRI=magnetic resonance imaging; N, n=number of participants

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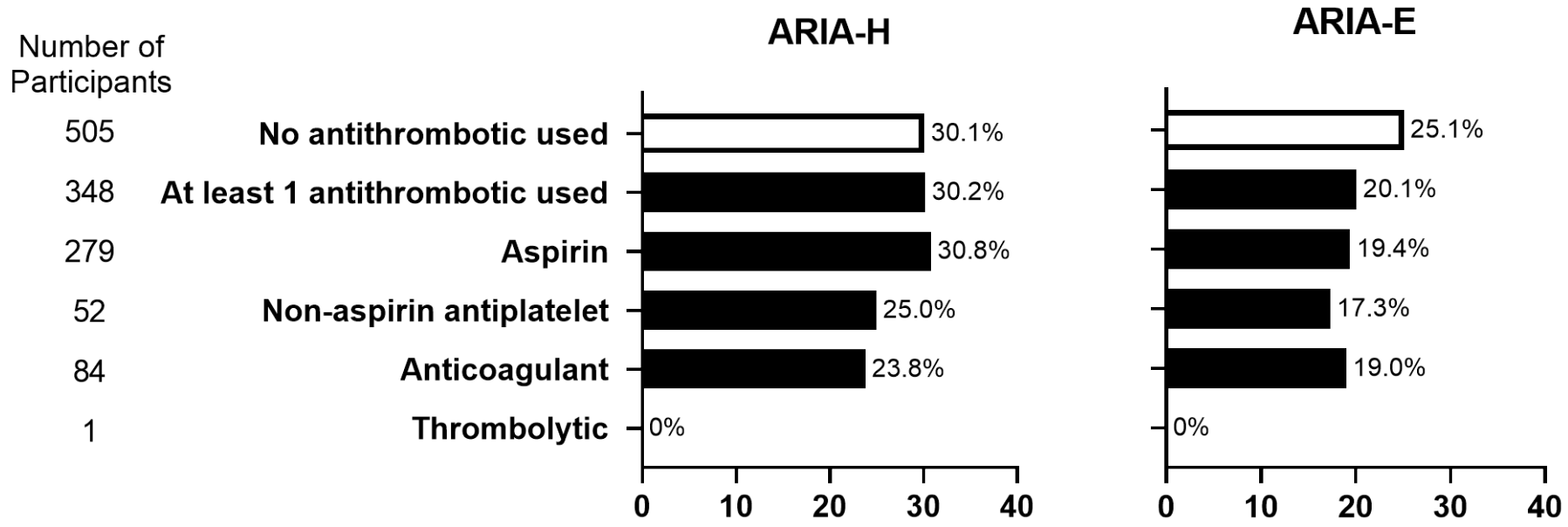
Antithrombotic use in ARIA events

- Antithrombotic use was permitted in TRAILBLAZER-ALZ 2
  - In the donanemab group, 9.8% of participants used anticoagulants[a] and 38.8% of participants used anti-platelets[b] in the double-blind period
- ARIA occurs at similar frequency with and without antithrombotic use



[a] Including heparins, warfarin, and direct oral anticoagulants
[b] Including aspirin and non-aspirin antiplatelets
[c] Participants were included in multiple subcategories if they had multiple antithrombotic use
[d] For participants who experienced multiple ARIA events, at least one ARIA event had antithrombotic use within 30 days prior to the event
Abbreviations: ARIA-E=amyloid-related imaging abnormalities-edema/effusions; ARIA-H=amyloid-related imaging abnormalities-hemorrhage/hemosiderin deposition

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IRR and immunogenicity

- IRRs in the donanemab group
  - Serious IRRs or hypersensitivity occurred in 3 participants (0.4%)
  - IRRs in most participants
    - were mild to moderate
    - occurred during or within 30 minutes of the end of the infusion
    - first occurred on infusion number 2 through 5
  - IRRs led to discontinuation of treatment in 3.6% of participants
- Immunogenicity in donanemab-treated participants
  - 87% had treatment-emergent antidrug antibodies
  - 84% were positive for neutralizing antibodies

TEAE PT n (%)	Placebo (N=874)	Donanemab (N=853)
IRR	4 (0.5)	74 (8.7)
Mild	3 (0.3)	42 (4.9)
Moderate	1 (0.1)	29 (3.4)
Severe	0 (0)	3 (0.4)
Hypersensitivity	2 (0.2)	10 (1.2)
Mild	2 (0.2)	3 (0.4)
Moderate	0 (0)	5 (0.6)
Severe	0 (0)	2 (0.2)
Anaphylactic reaction	0 (0)	3 (0.4)
Mild	0 (0)	1 (0.1)
Moderate	0 (0)	2 (0.2)
Severe	0 (0)	0 (0)

Abbreviations: IRR=infusion-related reaction; N, n=number of participants; PT=preferred term; TEAE=treatment-emergent adverse event

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Summary

- Safety profile was similar to the Phase 2 findings and consistent with class effects observed with amyloid plaque-lowering therapies.
- Mean changes in clinical laboratory values, vital signs, and ECGs were similar across treatment groups.
- Most frequently reported TEAEs that occurred more in the donanemab group include ARIA-H, ARIA-E, headache, IRR, and superficial siderosis of the CNS.
- The most common side-effect, ARIA-E, was typically transient and asymptomatic but serious and even fatal cases can occur. Careful safety monitoring is required to limit serious outcomes.

Abbreviations: ARIA-E=amyloid-related imaging abnormalities-edema/effusions; ARIA-H=amyloid-related imaging abnormalities-hemorrhage/hemosiderin deposition; CNS=central nervous system; ECG=electrocardiogram; IRR=infusion-related reaction, TEAE=treatment-emergent adverse event

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Donanemab in Early Symptomatic Alzheimer's Disease: Biomarker Results from TRAILBLAZER-ALZ 2

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Alzheimer's Association International Conference (AAIC)
Amsterdam, Netherlands, and Online
July 16 - 20, 2023

Sponsored by Eli Lilly and Company

Disclosures

- Oskar Hansson is/has been a board member for AC Immune, Amylyx, Alzpath, BioArctic, Biogen, Cerveau, Eisai, Eli Lilly and Company, Fujirebio, Merck, Novartis, Novo Nordisk, Roche, Sanofi, and Siemens.
- Amyvid (Florbetapir F 18) was developed at Avid Radiopharmaceuticals and is marketed by Eli Lilly and Company as a radioactive diagnostic agent for Positron Emission Tomography (PET) imaging of the brain to estimate β-amyloid neuritic plaque density; safety and effectiveness of Amyvid (Florbetapir F 18) has not been established for predicting development of dementia or other neurologic conditions and monitoring responses to therapies.
- Tauvid (Flortaucipir F 18) is approved for use with PET imaging of the brain to estimate the density and distribution of aggregated tau neurofibrillary tangles in adult patients with cognitive impairment who are being evaluated for Alzheimer's disease.
- All discussions refer to investigational purposes only.

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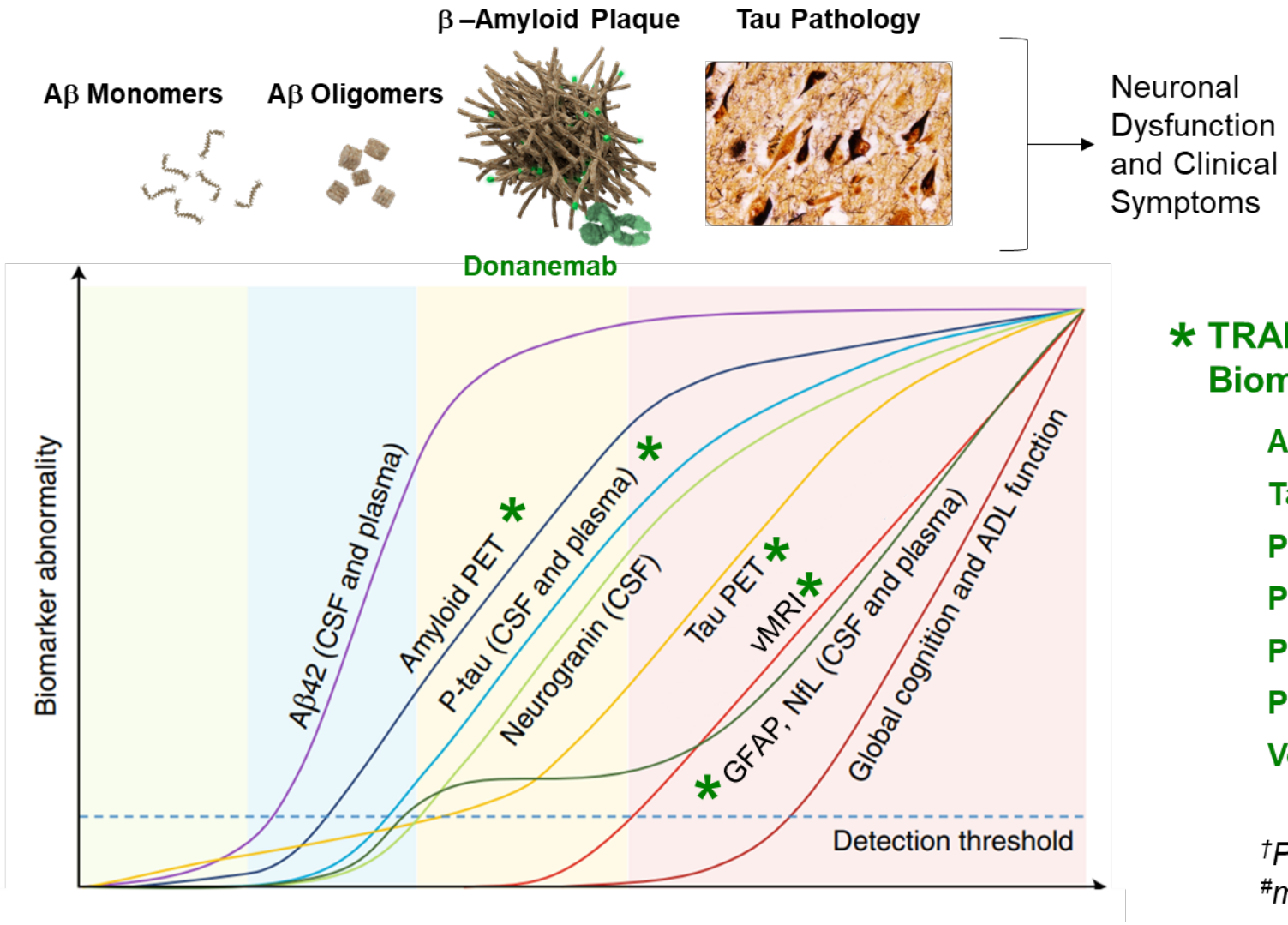
Alzheimer's Disease biomarker cascade



*** TRAILBLAZER-ALZ 2 Biomarker Outcomes:**

- **Amyloid PET†,#**
- **Tau PET†,#**
- **Plasma P-tau217†,#**
- **Plasma NfL†**
- **Plasma GFAP†**
- **Plasma P-tau181**
- **Volumetric MRI (vMRI)**

†Presented in this talk
#multiplicity-controlled testing

Image modified from Hansson O. Biomarkers for neurodegenerative diseases. Nat Med. 2021;27(6):954-963. doi:10.1038/s41591-021-01382-x
Abbreviations: CSF=cerebrospinal fluid; GFAP=glial fibrillary acidic protein; MRI=Magnetic Resonance Imaging; NfL=Neurofilament light chain; PET=positron emission tomography; P-tau181=phosphorylated tau 181; P-tau217=phosphorylated tau 217

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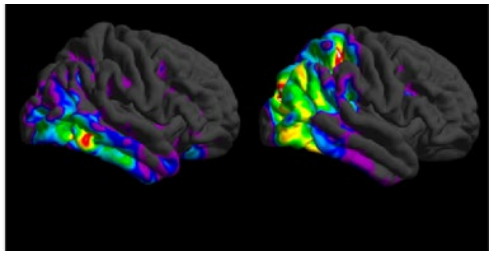
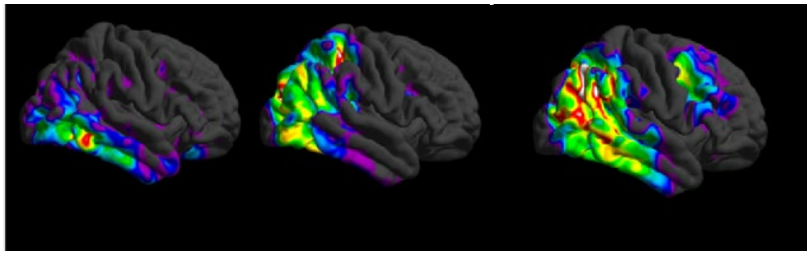
Baseline biomarkers

TRAILBLAZER-ALZ 2
Enrollment tau PET criteria:

Low-medium tau
1.10<SUVr≤1.46[#]



Low-medium tau
1.10<SUVr≤1.46[#]
+ High tau
+ >1.46 SUVr



	Low-medium Tau Population		Combined Population	
Biomarker	**Placebo (N=594)**	**Donanemab (N=588)**	**Placebo (N=876)**	**Donanemab (N=860)**
PET, mean (SD)*				
Amyloid PET Centiloids	101 (35)	102 (35)	102 (35)	104 (35)
Tau PET AD signature-weighted SUVr	1.21 (0.13)	1.21 (0.12)	1.35 (0.26)	1.34 (0.25)
Plasma[†], pg/mL mean (SD)				
P-tau217	5.4 (11.3)	6.6 (17.7)	6.8 (15.4)	7.5 (18.5)
NfL	21.8 (10.9)	22.7 (14.1)	22.3 (10.8)	22.9 (13.4)
GFAP	297 (170)	328 (390)	307 (205)	328 (348)

[#] Visual interpretation took precedence when highly discordant; *Screening values; [†]Actual N varies based on participants with missing values; TRAILBLAZER-ALZ 2 biomarker assays: C2N for P-tau217, Quanterix Simoa® for P-tau181, GFAP, and NfL Abbreviations: AD=Alzheimer's Disease; GFAP=glial fibrillary acidic protein; NfL=Neurofilament light chain; N=number of participants; PET=positron emission tomography; P-tau181=phosphorylated tau 181; P-tau217=phosphorylated tau 217; SD=standard deviation; SUVr=standardized uptake value ratio

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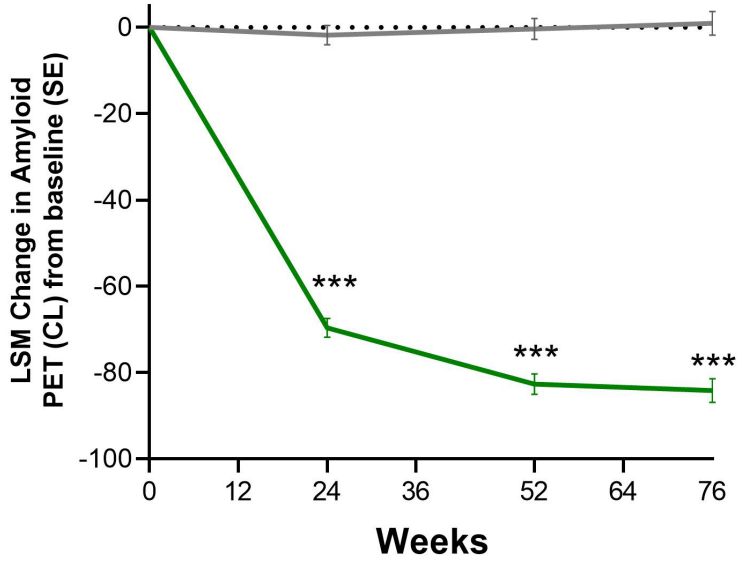
Donanemab reduced β-amyloid plaque in low-medium and combined tau populations, as measured by amyloid PET

Phase 2† Population

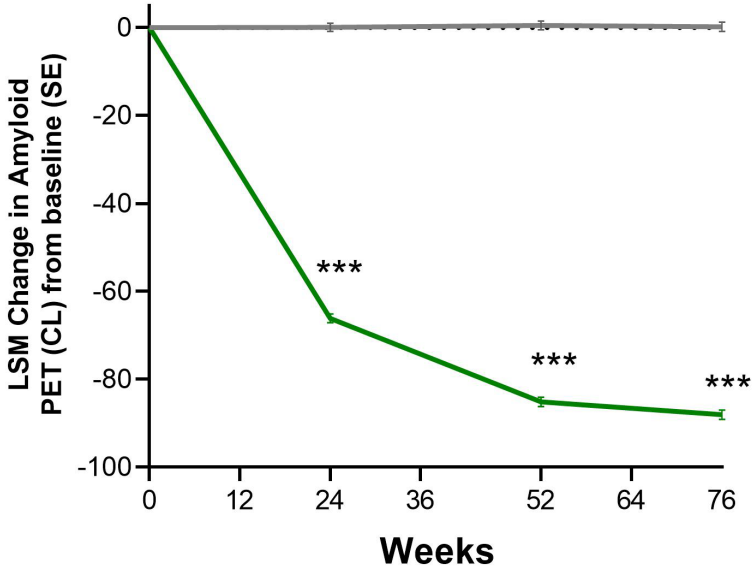
84 CL decrease by donanemab at 76 weeks



Pbo	n= 112	111	91	91
Dona	n= 121	115	92	90

Phase 3 Low-medium Tau Population

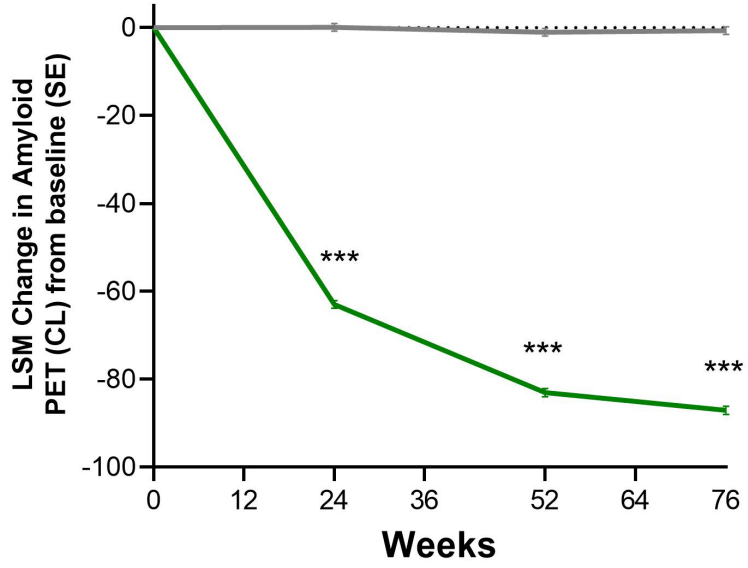
88 CL decrease by donanemab at 76 weeks



Pbo	n= 556	552	498	470
Dona	n= 525	521	463	433

Phase 3 Combined Population

87 CL decrease by donanemab at 76 weeks



Pbo	n= 812	805	729	690
Dona	n= 765	760	670	614

LSM, CL change from baseline, SE, and p-value asterisks are derived using mixed model repeated measures methodology with fixed factors for treatment, visit, treatment-by-visit interaction, and covariates for baseline score, baseline score-by-visit interaction, and age at baseline; ***p<0.0001. †Mintun, M. A. et al. N Engl J M, 2021; 384(18), 1691–1704. https://doi.org/10.1056/NEJMoa2100708. Abbreviations: CL=Centiloid; Dona=Donanemab; LSM=Least Squares Mean; n=number of participants; Pbo=Placebo; SE=Standard Error

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Amyloid reduction after donanemab treatment

Scan QR code for animation *or visit*
https://lillyscience.lilly.com/download/7sr30gxPcVNcFiW3hAwybJ?directdownload=true

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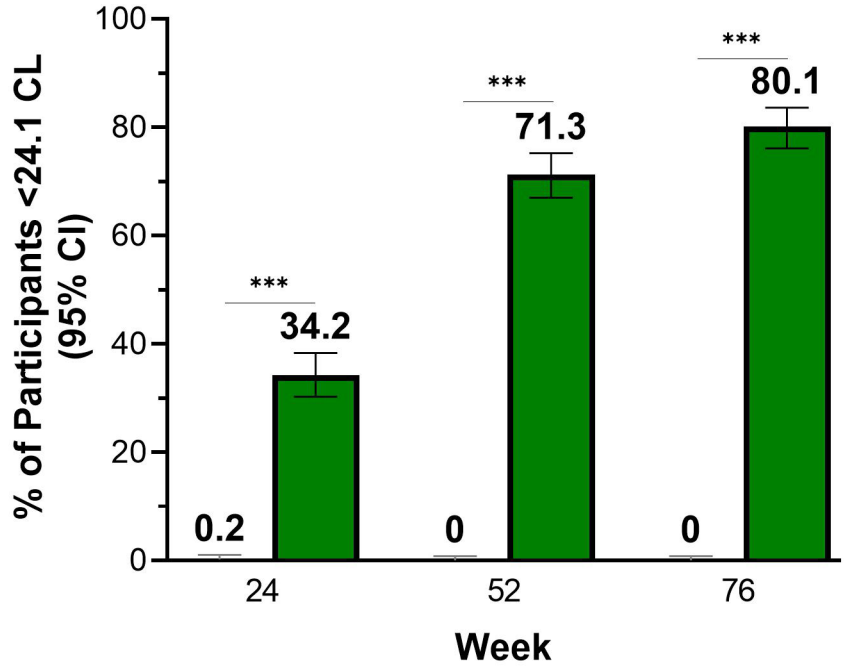
Donanemab treatment significantly cleared β-amyloid plaque in low-medium and combined tau populations

Low-medium Tau Population

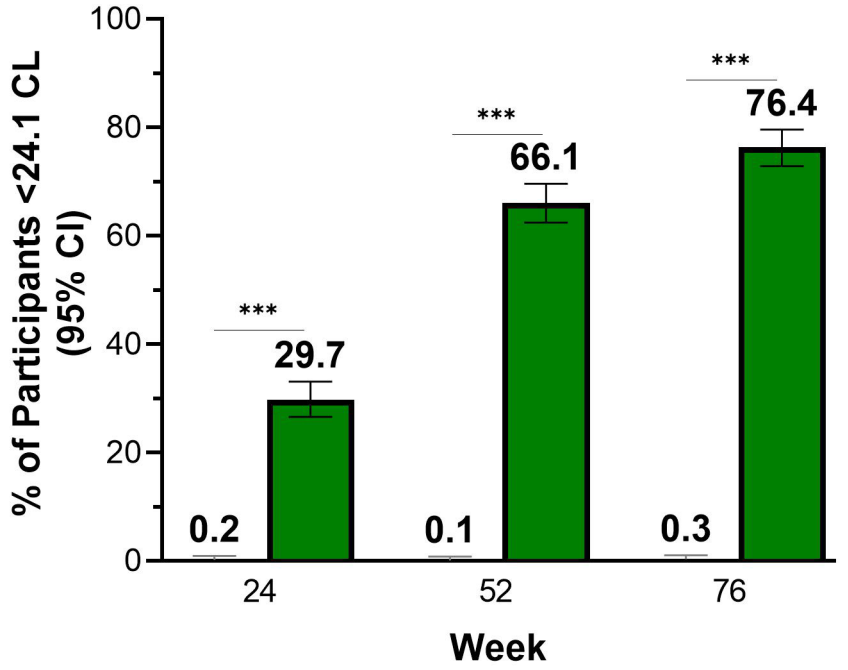
80% reached amyloid clearance by 76 weeks



Placebo	n= 553	498	470
Donanemab	n= 521	463	433

Combined Population

76% reached amyloid clearance by 76 weeks



Placebo	n= 805	730	690
Donanemab	n= 761	670	614

CI and p-value asterisks are derived using mixed model repeated measures methodology with fixed factors for treatment, visit, treatment-by-visit interaction, and covariates for baseline score, baseline score-by-visit interaction, and age at baseline; ***p<0.0001. Abbreviations: CL=Centiloid; CI=Confidence Intervals; n=number of participants

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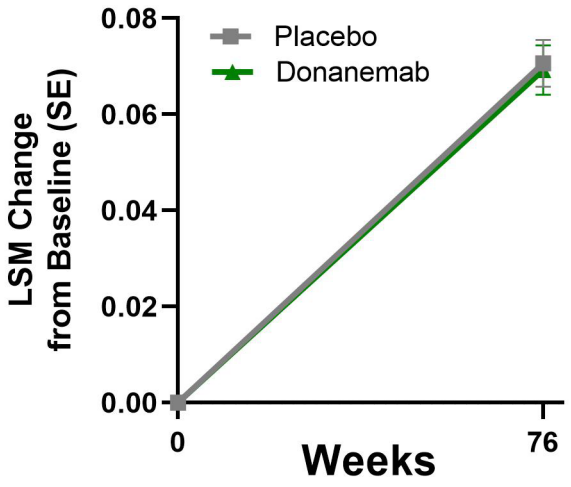
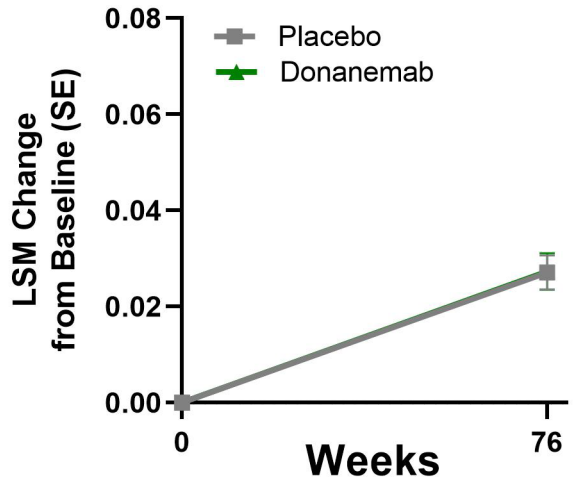
Donanemab treatment did not change AD signature-weighted or frontal tau PET SUVR

Low-medium Tau Population

AD signature-weighted SUVr

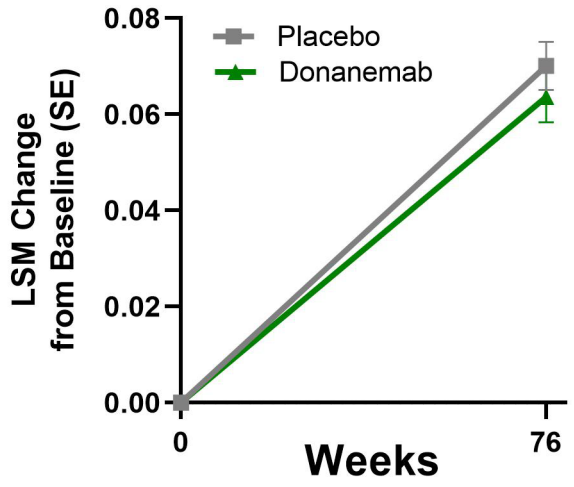


Frontal SUVr

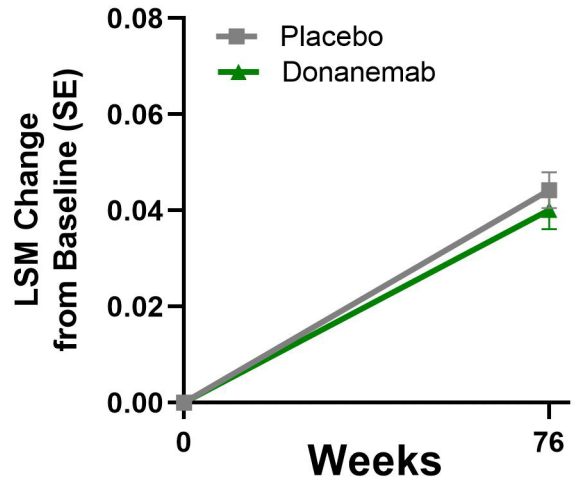


Combined Population

AD signature-weighted SUVr



Frontal SUVr



Placebo n=452	452	452	452	654	654	654	654
Donanemab n=404	404	404	404	578	578	578	578

Referenced to cerebellar crus; LSM change from baseline and SE derived using analysis of covariance model for endpoint measures with fixed factors for treatment, and covariates for baseline score and age, and for the combined population only, also tau burden. Abbreviations: AD=Alzheimer's disease; LSM=Least Squares Mean; n=number of participants; PET=Positron Emission Tomography; SE=Standard Error; SUVr=Standardized Uptake Value ratio

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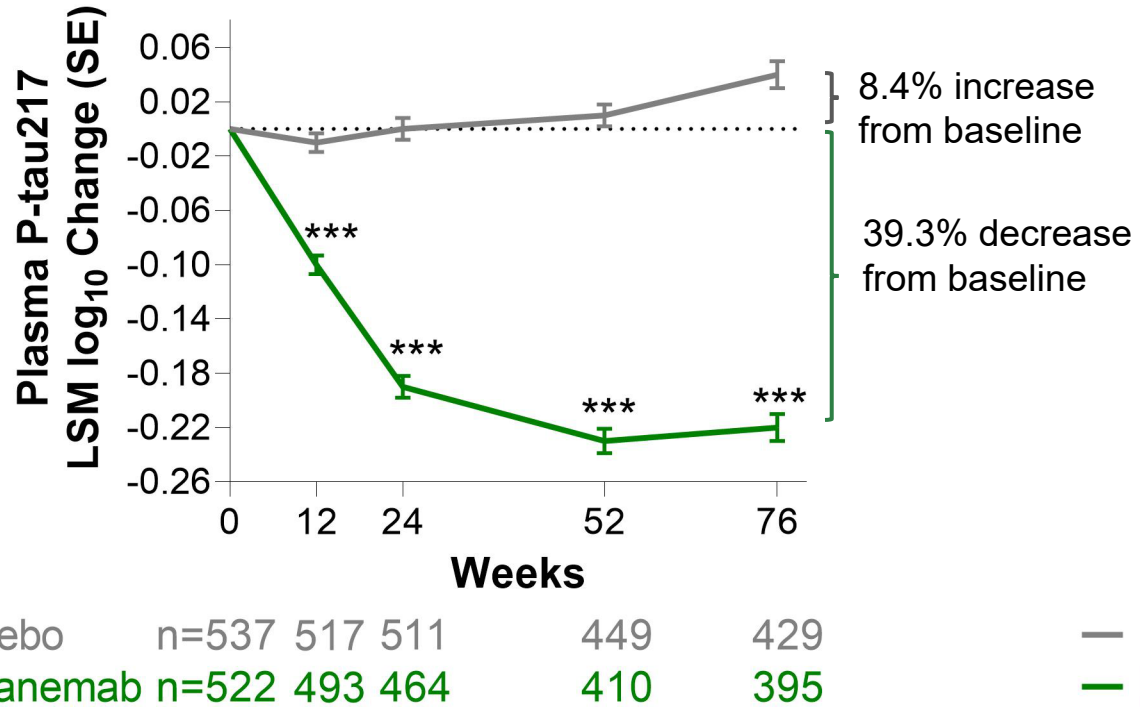
Donanemab treatment rapidly reduced plasma P-tau217

Low-medium Tau Population

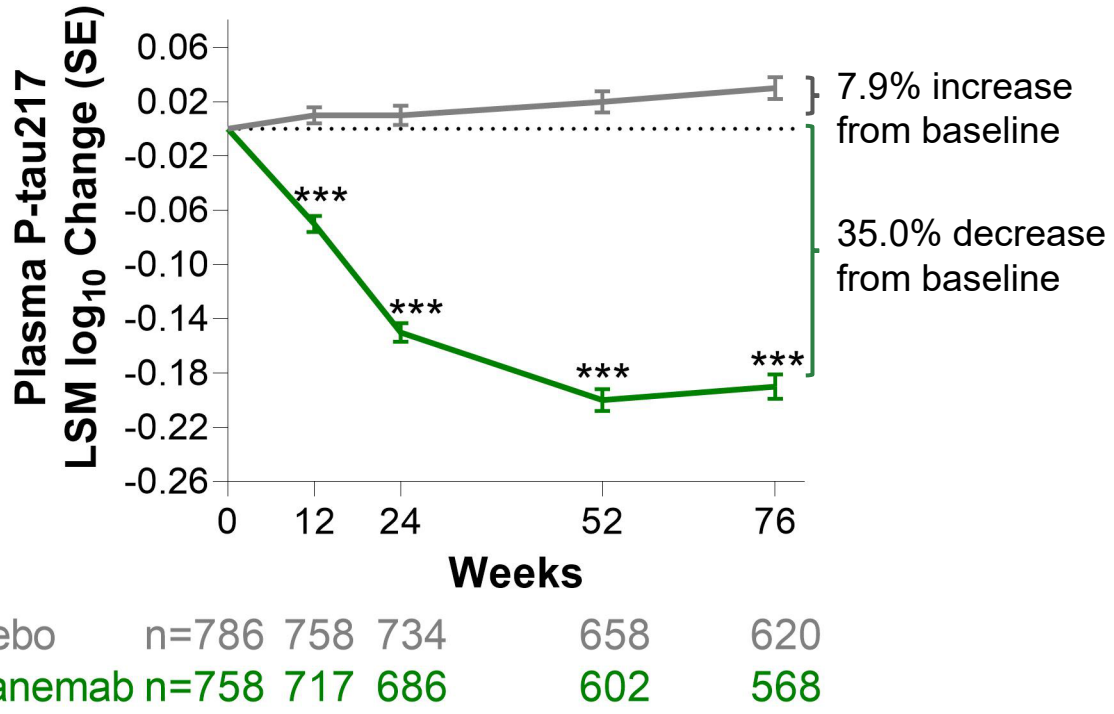
39% decrease by donanemab at 76w



Placebo	n=537	517	511	449	429
Donanemab	n=522	493	464	410	395

Combined Population

35% decrease by donanemab at 76w



Placebo	n=786	758	734	658	620
Donanemab	n=758	717	686	602	568

LSM change from baseline, SE, and p-value asterisks are derived using mixed model repeated measures methodology with fixed factors for treatment, visit, treatment-by-visit interaction, and covariates for baseline score, baseline score-by-visit interaction, and age at baseline; ***p<0.0001. C2N was used to assay plasma P-tau217. Abbreviations: LSM=Least Squares Mean; n=number of participants; P-tau217=phosphorylated tau 217; SE=Standard Error

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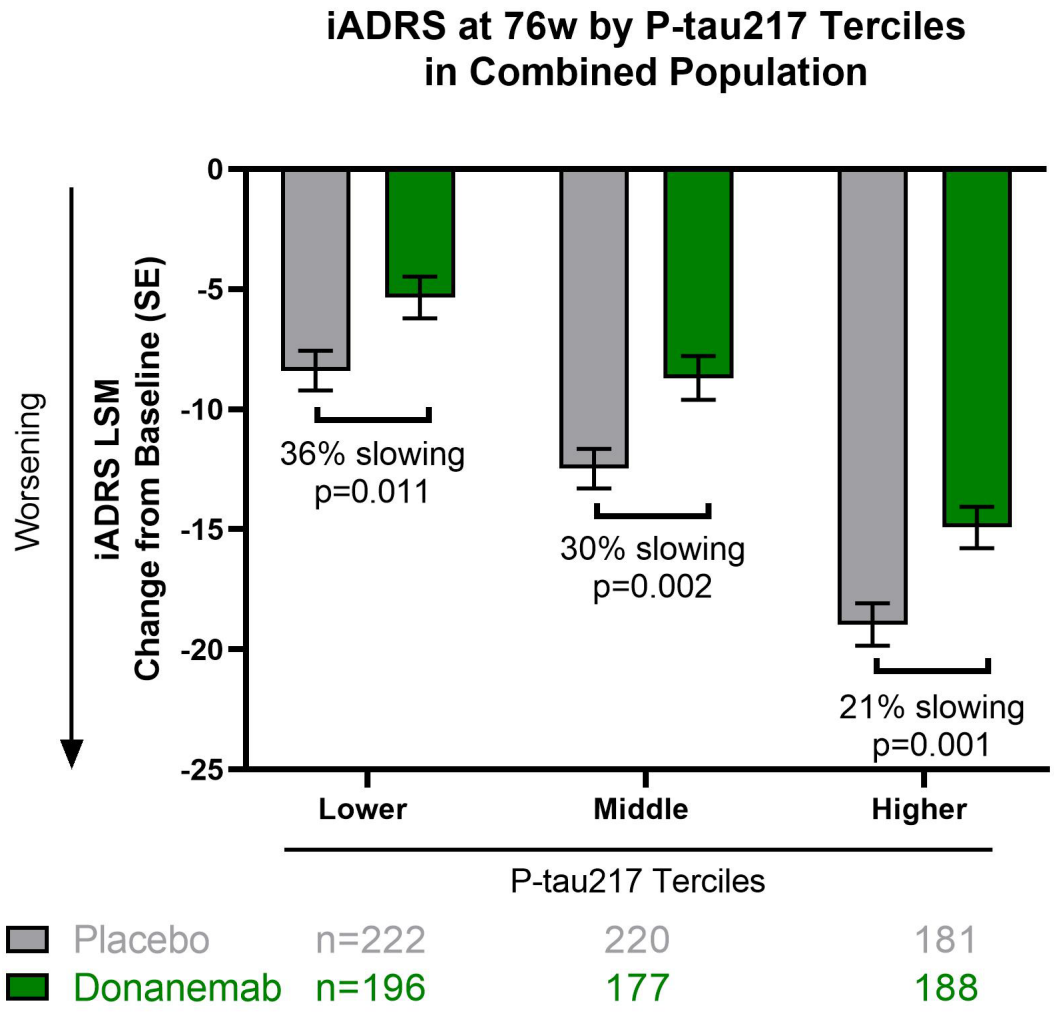
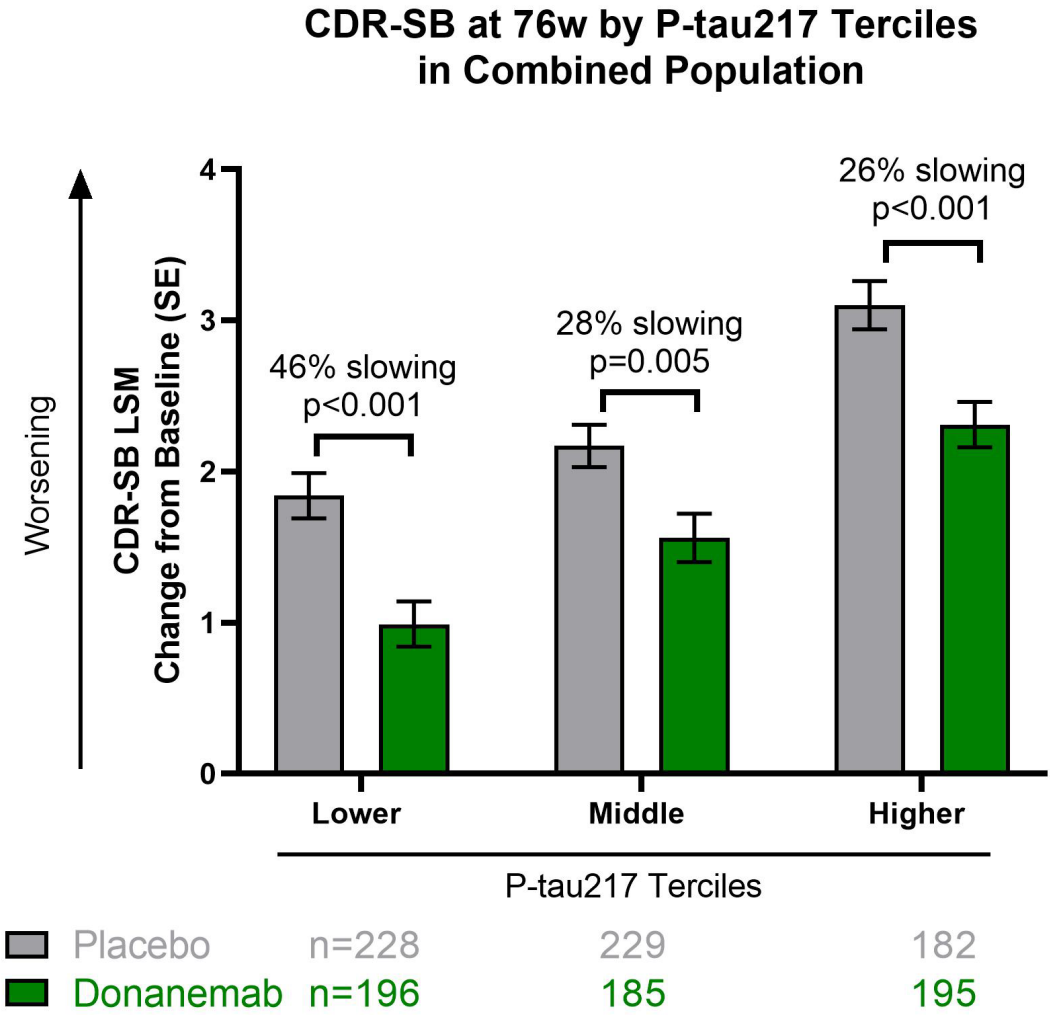
Post-hoc analysis: Participants with lowest baseline P-tau217 had better disease slowing by iADRS and CDR-SB





CDR-SB = Clinical Dementia Rating – Sum of Boxes; iADRS = Integrated Alzheimer's Disease Rating Scale; LSM = Least Squares Mean; n = number of participants; SE = Standard Error; w = weeks. LSM change from baseline, SE, and p-values are derived using natural cubic spline with 2 degrees of freedom methodology adjusted for basis expansion terms (two terms), basis expansion term-by-treatment interaction, and covariates for age at baseline, pooled investigator, baseline tau level, and baseline acetylcholinesterase inhibitor/memantine use. P-values are nominal.

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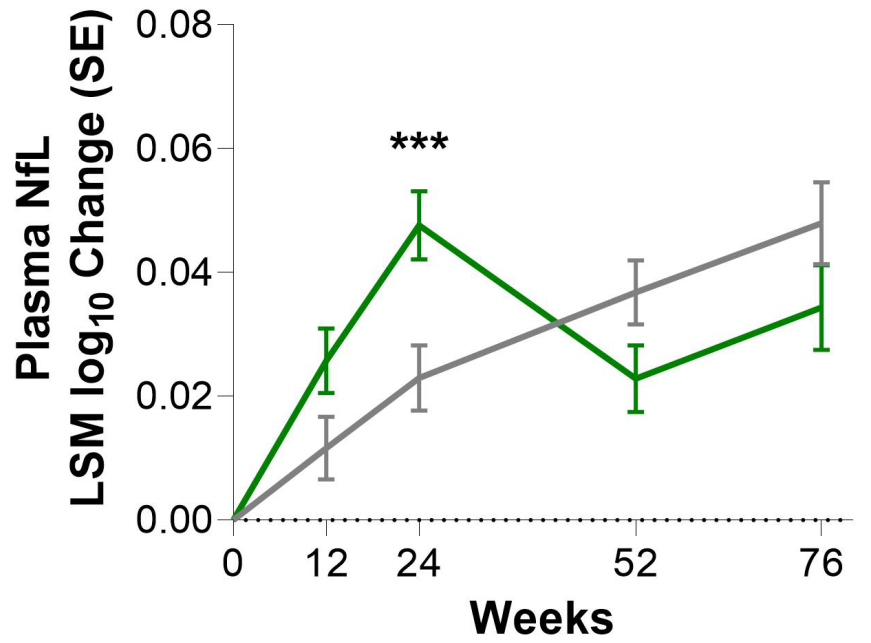
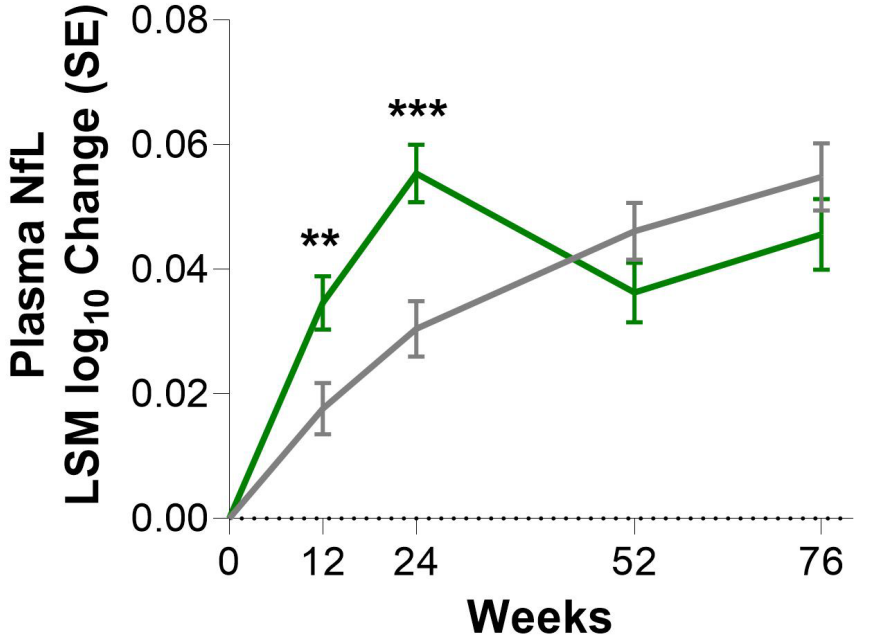
No clear pattern in plasma NfL over 76-week study

Low-medium Tau Population



Placebo	n=560	550	532	477	451
Donanemab	n=538	516	489	438	417

Combined Population



Placebo	n=824	806	772	697	653
Donanemab	n=783	750	719	635	592

LSM change from baseline, SE, and p-value asterisks are derived using mixed model repeated measures methodology with fixed factors for treatment, visit, treatment-by-visit interaction, and covariates for baseline score, baseline score-by-visit interaction, and age at baseline; **nominal p<0.01, ***nominal p≤0.001. Quanterix Simoa® was used to assay plasma NfL. Abbreviations: LSM=Least Squares Mean; NfL=Neurofilament light chain; n=number of participants; SE=Standard Error

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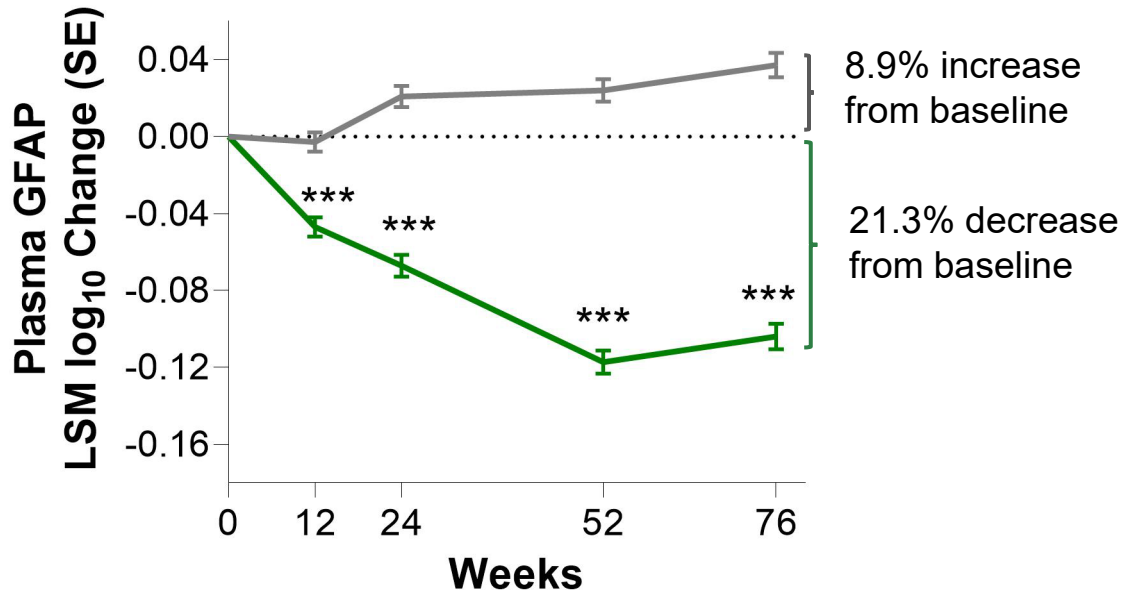
Donanemab treatment rapidly reduced plasma GFAP

Low-medium Tau Population

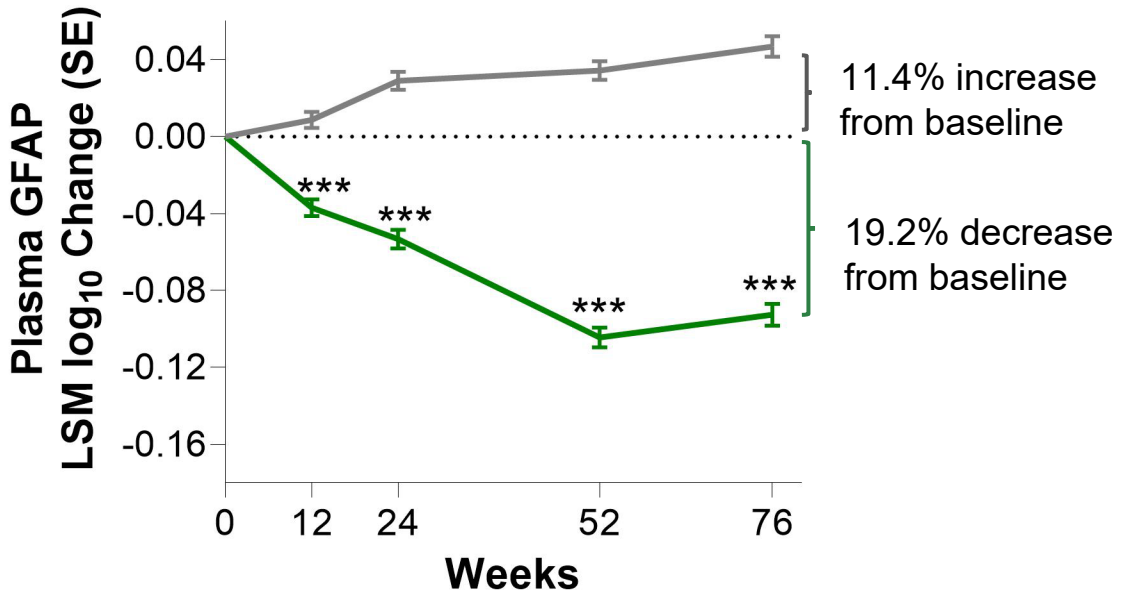
21% decrease by donanemab at 76w



Placebo	n=560	550	532	477	451
Donanemab	n=538	516	488	438	417

Combined Population

19% decrease by donanemab at 76w



Placebo	n=824	806	772	697	653
Donanemab	n=783	750	717	635	592

LSM change from baseline, SE, and p-value asterisks are derived using mixed model repeated measures methodology with fixed factors for treatment, visit, treatment-by-visit interaction, and covariates for baseline score, baseline score-by-visit interaction, and age at baseline; ***nominal p<0.0001. Quanterix Simoa® was used to assay GFAP. Abbreviations: GFAP=glial fibrillary acidic protein; LSM=Least Squares Mean; n=number of participants; SE=Standard Error; w=weeks

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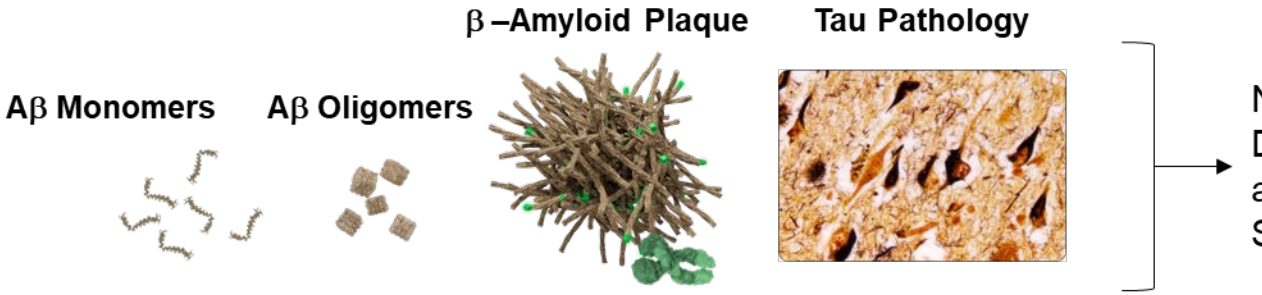
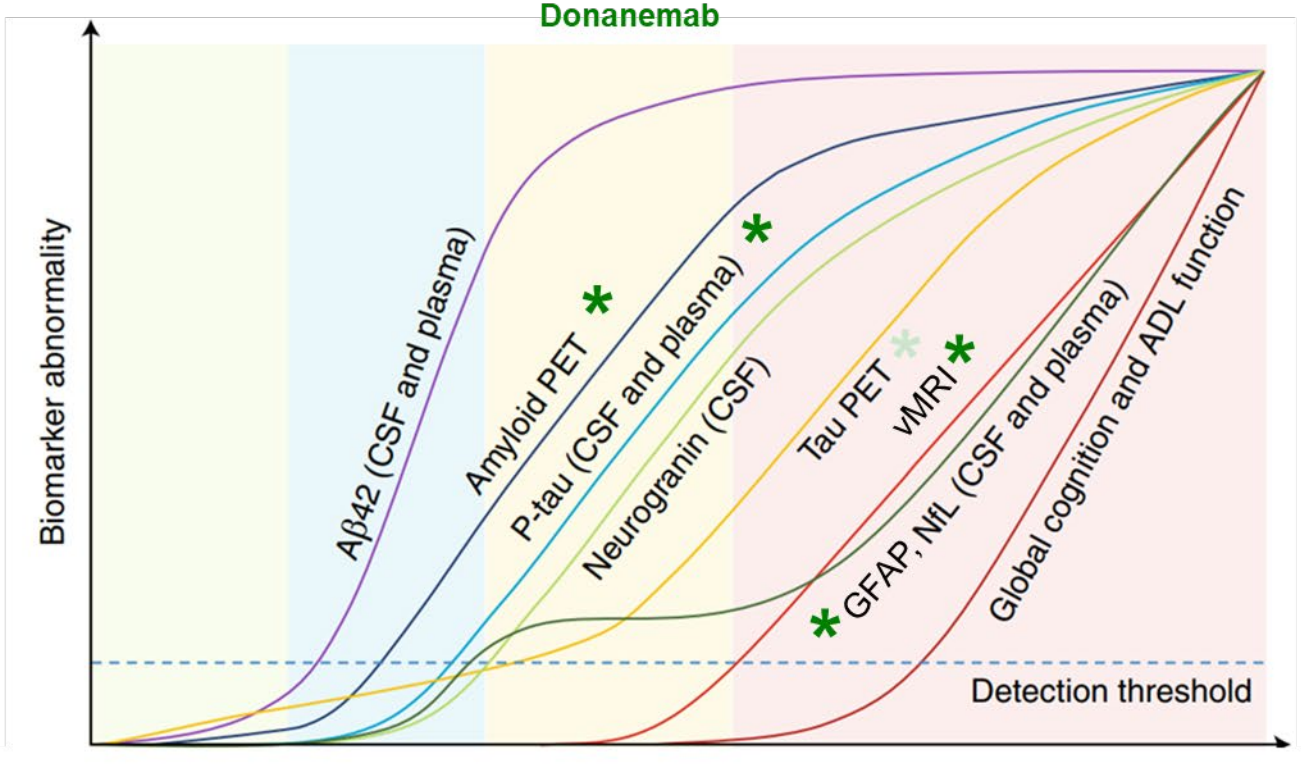
Summary of the effects of donanemab treatment





TRAILBLAZER-ALZ 2 Biomarker Outcomes:

- ⬇ Amyloid PET
- ⇔ Tau PET
- ⬇ Plasma P-tau217
- ⬍ Plasma NfL
- ⬇ Plasma GFAP

Plasma P-tau181 *and* ***vMRI*** *to be presented at "Amyloid reduction and evidence of downstream biomarker modification," Wednesday, 11:15am, Hall 5*

Image modified from Hansson O. Biomarkers for neurodegenerative diseases. Nat Med. 2021;27(6):954-963. doi:10.1038/s41591-021-01382-x
Abbreviations: CSF=cerebrospinal fluid; GFAP=glial fibrillary acidic protein; NfL=Neurofilament light chain; PET=positron emission tomography; P-tau181=phosphorylated tau 181; P-tau217=phosphorylated tau 217; vMRI=volumetric Magnetic Resonance Imaging

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Summary

- Donanemab significantly reduced brain amyloid plaque, plasma P-tau217, and GFAP at the earliest post-baseline study timepoint measured (12 weeks for plasma and 24 weeks for PET) and within an 18-month timeframe.
- Over 66% and 76% of trial participants with symptomatic Alzheimer's disease achieved amyloid clearance at 52 weeks and 76 weeks, respectively.
- Frontal Tau PET difference from placebo was not replicated from the phase 2 TRAILBLAZER-ALZ study and was the only gated outcome out of the 24 pre-specified gated outcomes that was not significant.
- Donanemab treatment on vMRI, P-tau181, and the correlation between amyloid reduction and clinical scale to be presented at "Amyloid reduction and evidence of downstream biomarker modification," Wednesday, 11:15am, Hall 5.

Abbreviations: GFAP=glial fibrillary acidic protein; PET=positron emission tomography; P-tau181=phosphorylated tau 181; P-tau217=phosphorylated tau 217; vMRI=volumetric Magnetic Resonance Imaging.

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The Clinical Relevance of the TRAILBLAZER-ALZ 2 Findings

Liana G Apostolova

Indiana University School of Medicine, Indianapolis, IN, USA

Alzheimer's Association International Conference (AAIC)
Amsterdam, Netherlands, and Online
July 16 - 20, 2023

Sponsored by Eli Lilly and Company

Disclosures

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- LEADS (NIA U01 AG057195) is supported by AVID Pharmaceuticals, Life Molecular Imaging, Roche Diagnostics and Eli Lilly and Company
- Consulting - Biogen, Eli Lilly and Company, Eisai, GE Healthcare, Roche, Genentech, Siemens, Alnylam, Corium and Prothena

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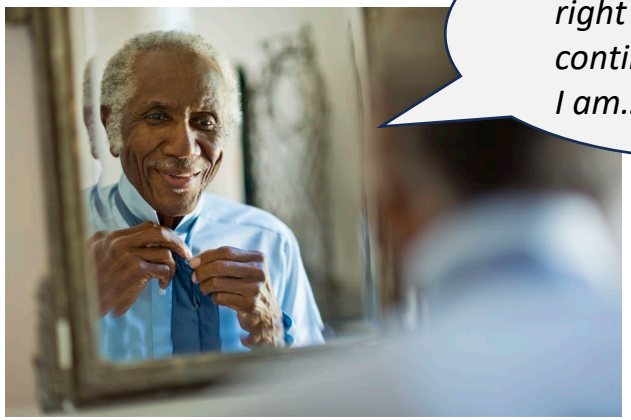
What Matters Most to Patients and Care Partners?

- Individuals experiencing early symptoms are concerned about:[1]
  - Memory (80%)
  - Dependence (67%)
- Most desired outcomes of AD treatment are:[1]
  - Improvement or restoration of memory (67%)
  - Stopping (58%) or slowing (33%) AD progression
  - Maintaining ability to function, perform ADLs (25%)
- A wide range of other items beyond cognition and functional ability are also viewed as important - emotional well-being, a desire to preserve independence, overall physical and mental health, and safety[2-5]

"Ideally it would just stop the memory loss. I could definitely live and survive the way I am now. But you don't know what's going to happen in the future, how it progresses." (patient)[1]



"If they could stop it right now, then I could continue to function like I am….." (patient)[1]

[1]DiBenedetti et al Alzheimers Res & Ther 2020;12:90; [2]Hauber et al Neurol Ther 2023;12:505–527; [3]Jessen et al J Prev Alz Dis 2022;9:550-555;
[4]Watson et al Health Expectations 2019 22:504-517
Abbreviations: AD=Alzheimer's disease; ADLs=activities of daily living

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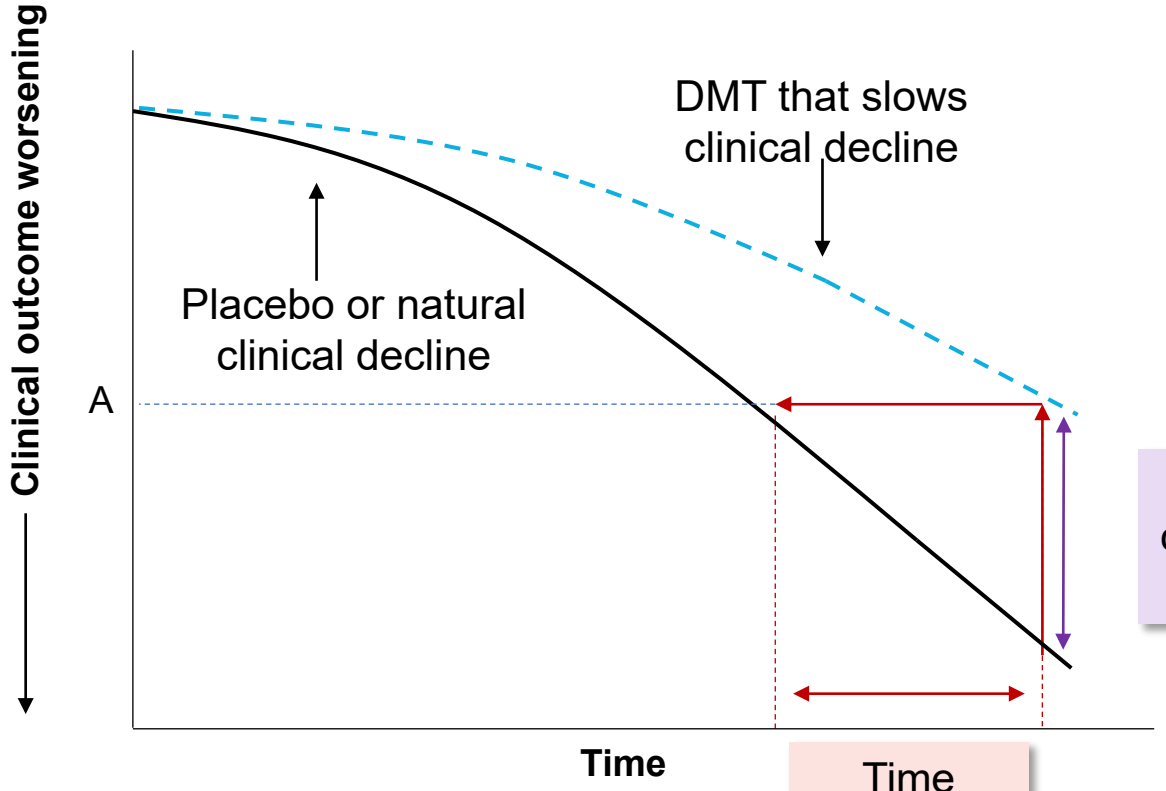
Interpreting Treatment Effect through ‘Time Saved’



In TRAILBLAZER-ALZ 2, donanemab treatment slowed clinical decline by 35%, based on iADRS

DMT effect on clinical outcome measure

Expressed as the *point difference* between treatment and placebo groups or *% slowing*

The time saving approach expresses treatment effect as *time saved* with treatment

Time saved with DMT

Dickson et al J Prev Alz Dis 2023;10:595-599

Abbreviations: DMT=disease-modifying therapy; iADRS=integrated Alzheimer’s Disease Rating Scale

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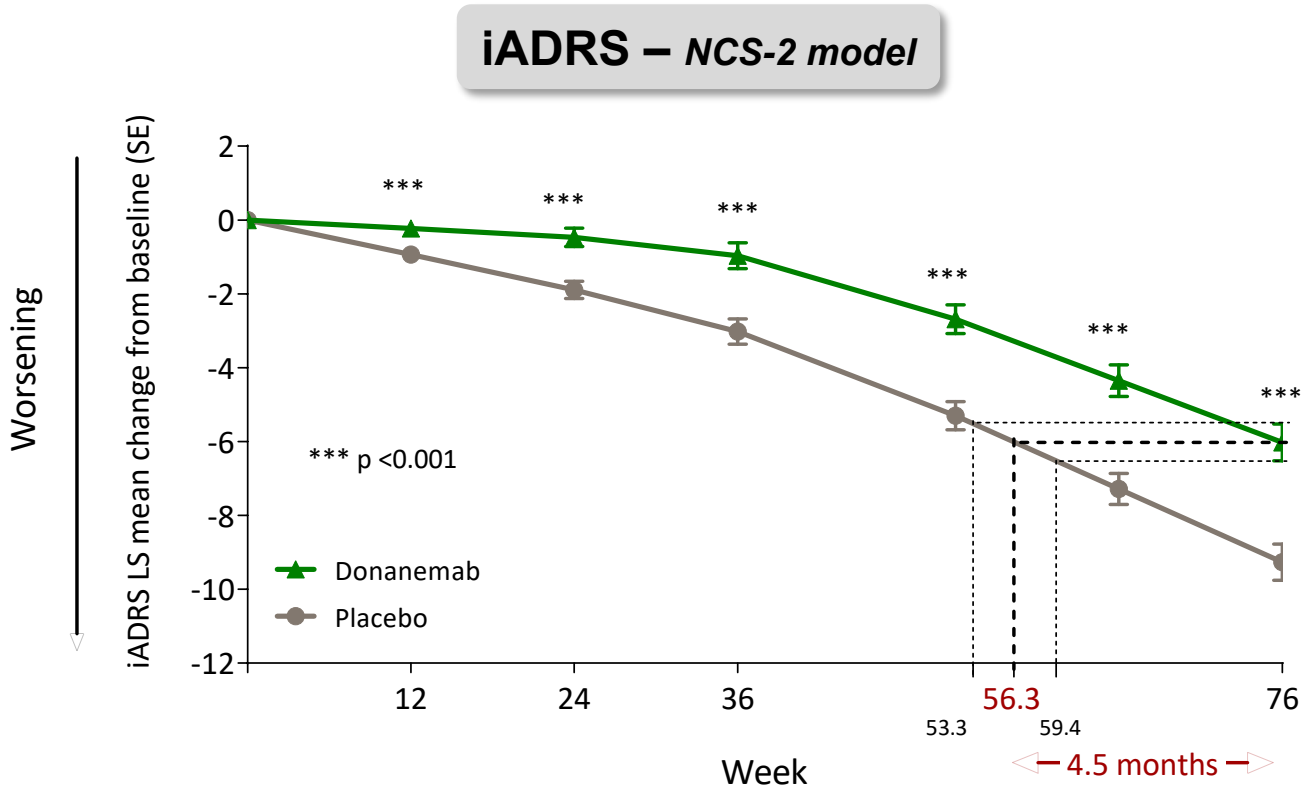
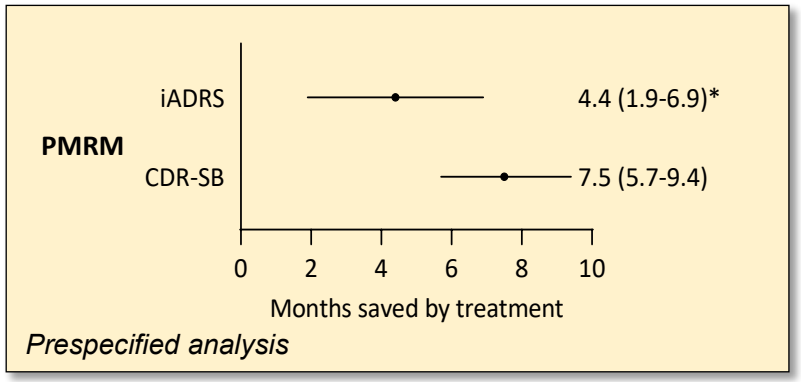
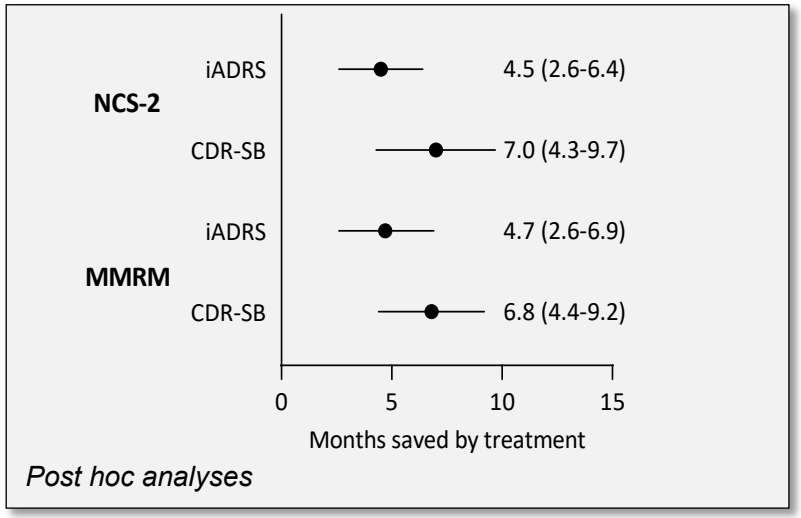
Phase 3 TRAILBLAZER-ALZ 2: Time Saved with Donanemab (low-medium tau population)







Across statistical approaches and outcome measures, donanemab treatment resulted in 4.4 – 7.5 months *saved* (i.e., delay in clinical decline) at 18 months

PMRM proportionality of time slowing was valid and utilized for CDR-SB, but not utilized for iADRS
*mean (95% confidence interval)

Abbreviations: CDR-SB=Clinical Dementia Rating-Sum of Boxes; iADRS=integrated Alzheimer's Disease Rating Scale; MMRM=mixed model repeated measures; LS=least sum of squares; NCS-2=Natural cubic spline model with 2 degrees of freedom; PMRM=Progression Model for Repeated Measures; SE=standard error

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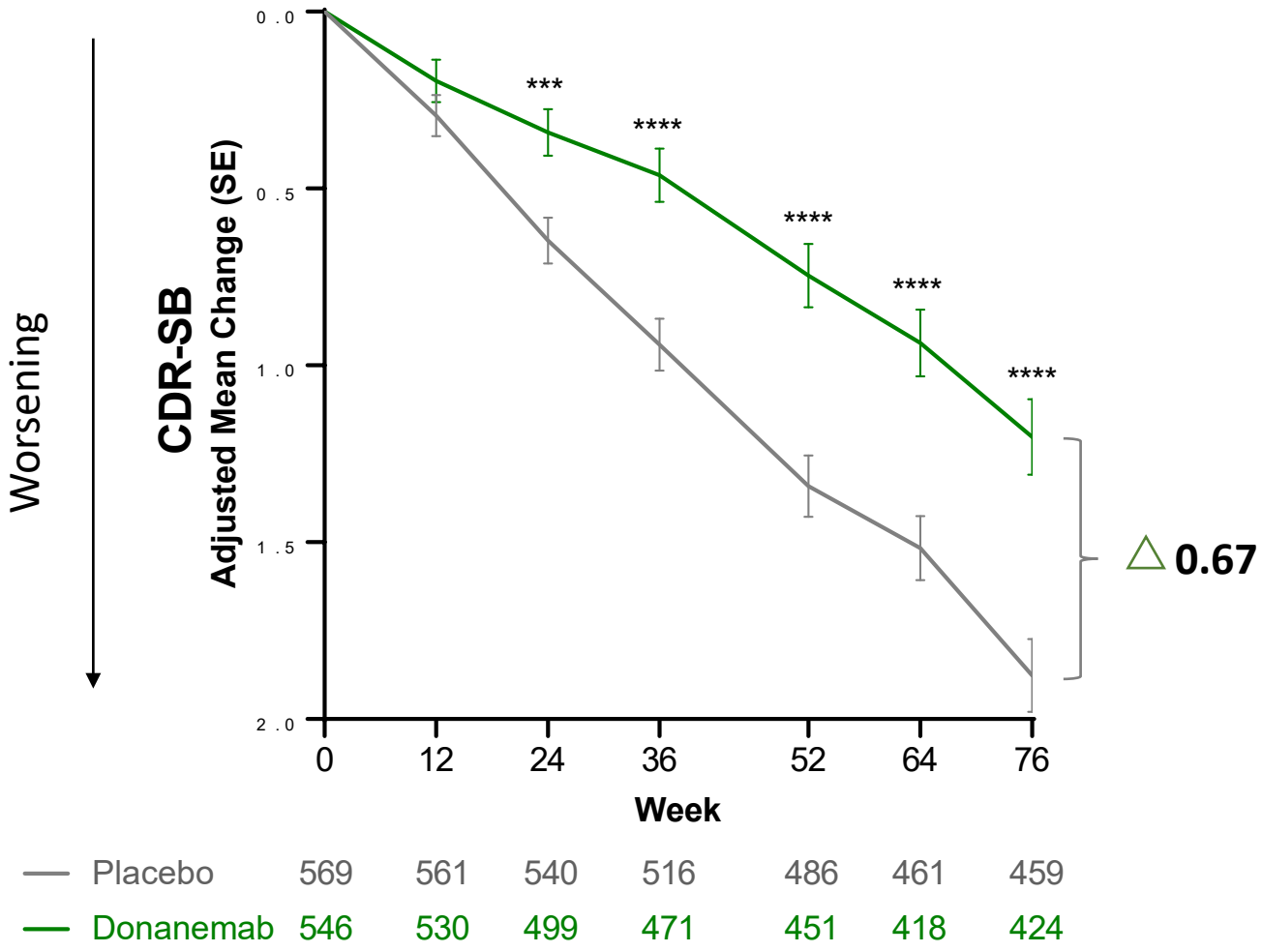
Phase 3 TRAILBLAZER-ALZ 2: CDR-SB (low-medium tau population)



0.67-point difference between donanemab and placebo at 76 weeks

*** P<0.001, **** P<0.0001
Abbreviations: CDR-SB=Clinical Dementia Rating–Sum of Boxes; SE=Standard Error

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Clinical Dementia Rating-Sum of Boxes

CLINICAL DEMENTIA RATING (CDR) – *score calculated by adding box scores*

	0 = None	0.5 = Questionable	1 = Mild	2 = Moderate	3 = Severe
Memory	No memory loss or slight inconsistent forgetfulness	Consistent slight forgetfulness; partial recollection of events; "benign" forgetfulness	Moderate memory loss; more marked for recent events; defect interferes with everyday activities	Severe memory loss; only highly learned material retained; new material rapidly lost	Severe memory loss; only fragments remain
Orientation	Fully oriented	Fully oriented except for slight difficulty with time relationships	Moderate difficulty with time relationships; oriented for place at examination; may have geographic disorientation elsewhere	Severe difficulty with time relationships; usually disoriented to time, often to place	Oriented to person only
Judgment & Problem Solving	Solves everyday problems & handles business & financial affairs well; judgment good in relation to past performance	Slight impairment in solving problems, similarities, and differences	Moderate difficulty in handling problems, similarities, and differences; social judgment usually maintained	Severely impaired in handling problems, similarities, and differences; social judgment usually impaired	Unable to make judgments or solve problems
Community Affairs	Independent function at usual level in job, shopping, volunteer and social groups	Slight impairment in these activities	Unable to function independently at these activities although may still be engaged in some; appears normal to casual inspection	Appears well enough to be taken to functions outside a family home	Appears too ill to be taken to functions outside a family home
Home and Hobbies	Life at home, hobbies, and intellectual interests well maintained	Life at home, hobbies, and intellectual interests slightly impaired	Mild but definite impairment of function at home; more difficult chores abandoned; more complicated hobbies and interests abandoned	Only simple chores preserved; very restricted interests, poorly maintained	No significant function in home
Personal Care	Fully capable of self-care		Needs prompting	Requires assistance in dressing, hygiene, keeping of personal effects	Requires much help with personal care; frequent incontinence

Hughes et al Br J Psychiatry 1982;140:566-572
Morris Neurology 1993;43:2412-2414

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Clinical Dementia Rating-Sum of Boxes

CDR-SB					
	0 = None	0.5 = Questionable	1 = Mild	2 = Moderate	3 = Severe
Memory		Consistent slight forgetfulness; partial recollection of events; “benign” forgetfulness	Moderate memory loss; more marked for recent events; defect interferes with everyday activities		
Judgment & Problem Solving		Slight impairment in solving problems, similarities, and differences	Moderate difficulty in handling problems, similarities, and differences; social judgment usually maintained		
Community Affairs		Slight impairment in these activities	Unable to function independently at these activities although may still be engaged in some; appears normal to casual inspection		

Hughes et al Br J Psychiatry 1982;140:566-572
Morris Neurology 1993;43:2412-2414
Abbreviations: CDR-SB=Clinical Dementia Rating-Sum of Boxes

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Phase 3 TRAILBLAZER-ALZ 2: No decline on the CDR-SB (low-medium tau population)

At 24 weeks — p=0.012

0.51 donanemab **0.43** placebo

At 52 weeks* — p<0.001

0.47 donanemab **0.29** placebo

At 76 weeks — p=0.006

0.32 donanemab **0.24** placebo

*gated endpoint

- Participants in the donanemab group had a significantly greater estimated probability of no decline on CDR-SB vs those in the placebo group
- Represents disease stability at given timepoint compared to baseline

Abbreviations: CDR-SB=Clinical Dementia Rating–Sum of Boxes

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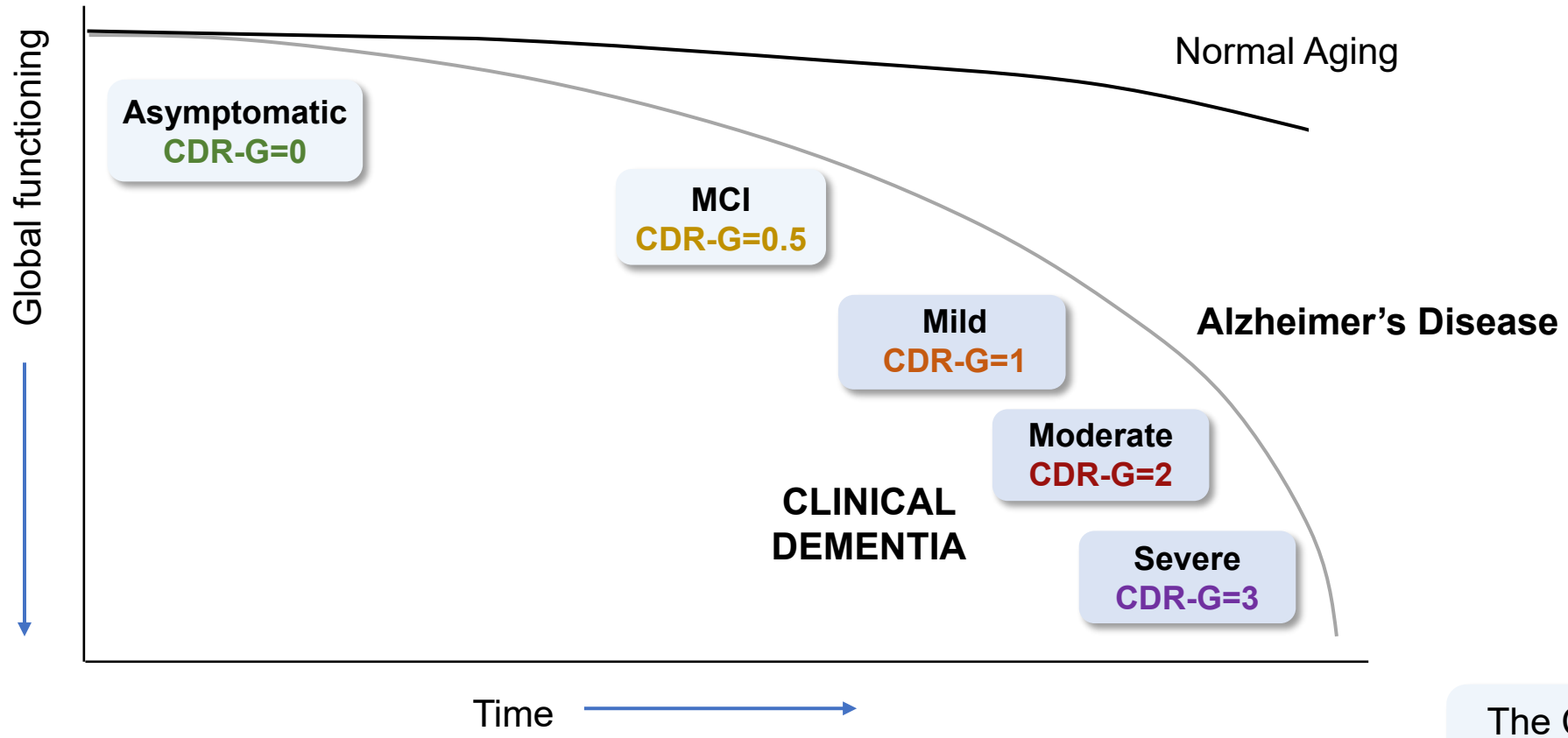
CDR-Global Score: Progression to next clinical stage



The CDR-G score is calculated using an algorithm

Sperling et al Alzheimer's Dement 2011;7:280-292
Coley et al Alzheimer's Dement 2011;7:602-610
Cedarbaum et al Alzheimers Dement. 2013;9(1 Suppl):S45-S55
Abbreviations: CDR-G=Clinical Dementia Rating-Global Scale

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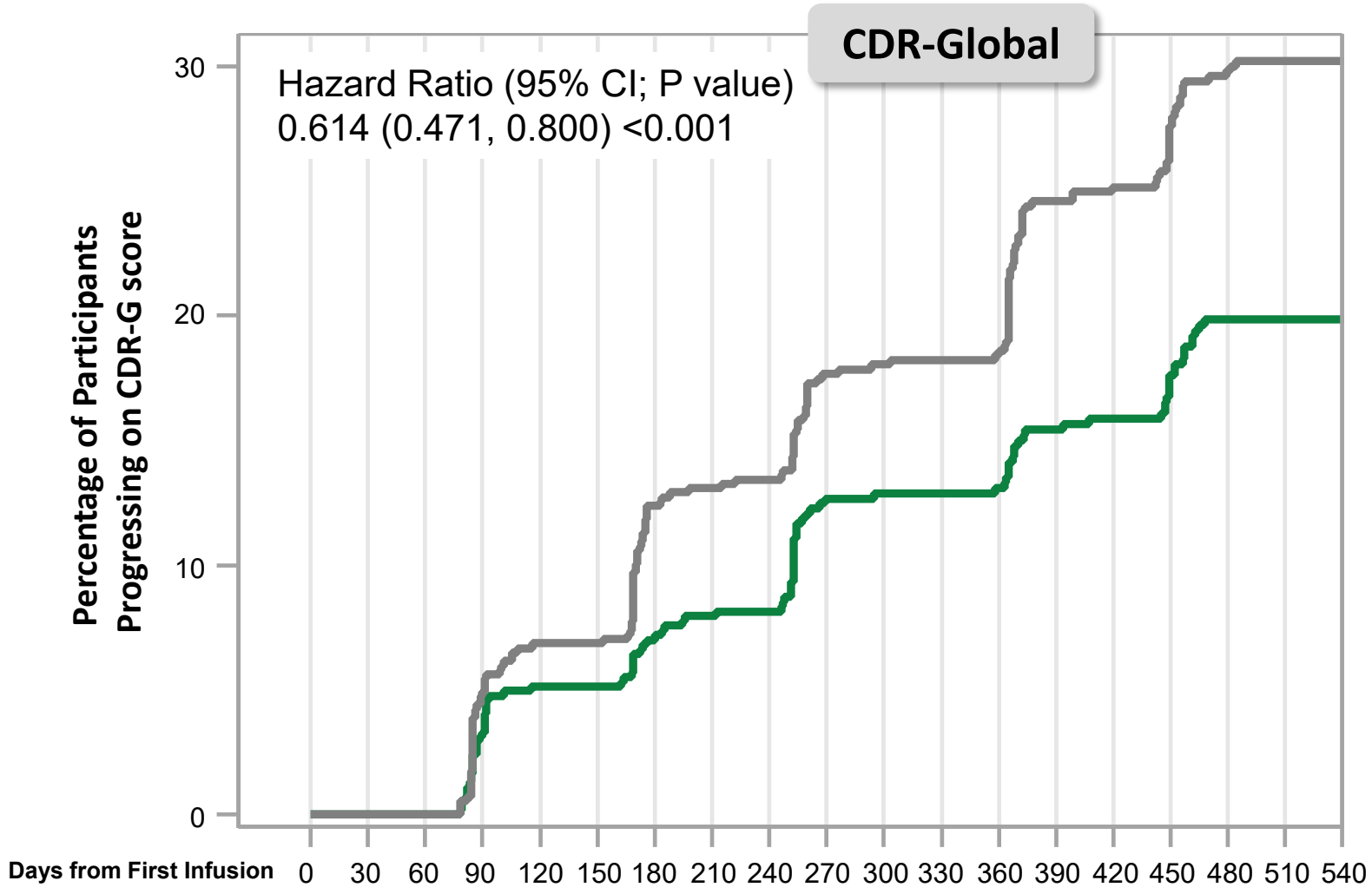
Phase 3 TRAILBLAZER-ALZ 2: Risk reduction for progression to next clinical stage (low-medium tau population)



38.6% lower risk of progression over 76 weeks

	Placebo	Donanemab
N	573	555
Event	163	100
Time	% (SE) n at risk	% (SE) n at risk
60 days	0.0 (0.00) 570	0.0 (0.00) 552
120 days	6.8 (1.06) 529	5.1 (0.94) 514
180 days	12.4 (1.38) 489	7.2 (1.11) 492
240 days	13.4 (1.44) 474	8.1 (1.18) 470
360 days	18.6 (1.65) 425	13.1 (1.47) 412
480 days	29.8 (1.98) 345	19.9 (1.79) 335

Definition of event: an increase from baseline in CDR-G score at two consecutive visits. Hazard ratio and P-value were generated using a Cox proportional hazards model adjusted for baseline age, baseline value, and baseline acetylcholinesterase inhibitor/memantine use and stratified by pooled investigator.
Abbreviations: CDR-G= Clinical Dementia Rating-Global Scale; CI=confidence interval; N=number of participants; SE=standard error

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Meaningful Change for Individual Patients

- Meaningful Within-Patient Change = threshold at which well-being of patient and/or their care partner is notably impacted (i.e., clinically meaningful worsening of symptoms)
- This threshold is used for the evaluation of *individual patient* change but not for interpreting between group differences

Meaningful Within-Patient Change

iADRS

At 2 consecutive visits, worsening from baseline of:

- ≥ *5 points* *(participants with MCI)*
- ≥ *9 points* *(participants with mild dementia*)*

CDR-SB

At 2 consecutive visits, worsening from baseline of:

- ≥ *1 point* *(participants with MCI)*
- ≥ *2 points* *(participants with mild dementia*)*

*due to Alzheimer's disease; Wessels et al Alzheimer's Dementia 2022;8:e12312; Andrews et al Alzheimer's Dementia 2019;5:354-363; Lansdall et al J Prev Alzheimers Dis 2019;6 (suppl1)

Abbreviations: CDR-SB=Clinical Dementia Rating-Sum of Boxes; iADRS=integrated Alzheimer's Disease Rating Scale; MCI=mild cognitive impairment

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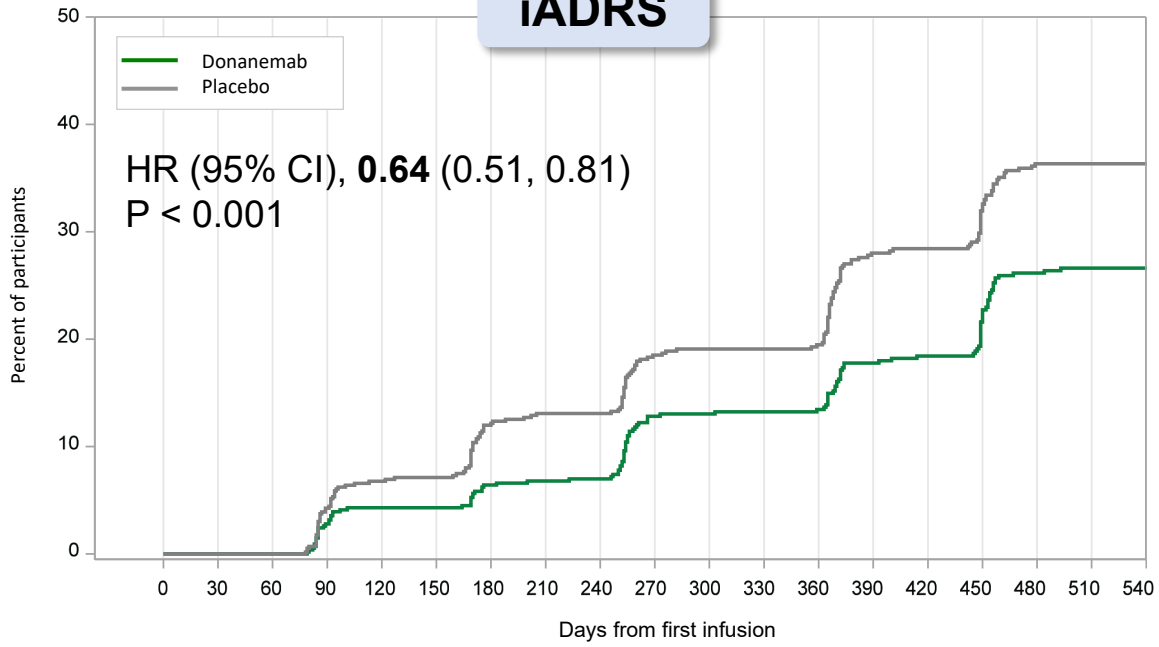
Phase 3 TRAILBLAZER-ALZ 2: Risk of meaningful within-patient change (low-medium tau population)

iADRS

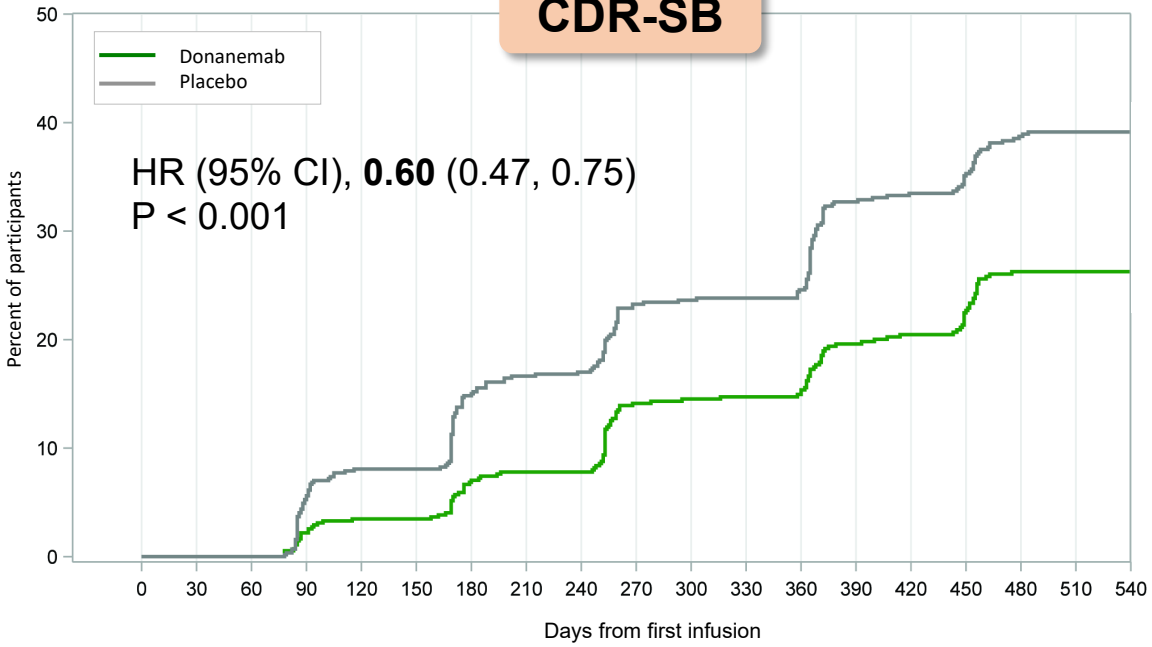


Weeks	12	24	36	52	64	76

36% lower risk of a meaningful within-patient change over 76 weeks with donanemab treatment

**meaningful within-patient change : An iADRS change of ≥ -5 points for MCI due to AD and ≥ -9 points for mild AD dementia at 2 consecutive visits from baseline*

CDR-SB



Weeks	12	24	36	52	64	76

40% lower risk of a meaningful within-patient change over 76 weeks with donanemab treatment

**meaningful within-patient change: A CDR-SB change of ≥ 1 point for MCI due to AD and ≥ 2 points for mild AD dementia at 2 consecutive visits from baseline*

Abbreviations: AD=Alzheimer's disease; CDR-SB= Clinical Dementia Rating-Sum of Boxes; CI=confidence interval; HR=hazard ratio; iADRS= integrated Alzheimer's Disease Rating Scale; MCI=mild cognitive impairment

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Summary

- In this presentation, the clinical relevance of donanemab treatment has been shown by:
  - ***Slowing of clinical decline***

    Donanemab treatment saved 4.4 - 7.5 months over the course of 18 months
  - ***Stability of clinical symptoms***

    Estimated probability of no change in the CDR-SB (no clinical decline) at one year significantly higher for participants receiving donanemab (0.47) versus placebo (0.29)
  - ***Lower risk of advancement to next clinical stage***

    39% lower risk of progressing to the next clinical stage of disease with donanemab treatment versus placebo
  - ***Lower risk of meaningful within-patient change***

    36 - 41% reduction in risk of experiencing a meaningful decline with donanemab treatment

Abbreviations: CDR-SB=Clinical Dementia Rating-Sum of Boxes

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TRAILBLAZER-ALZ 2 Session Conclusions

- Findings from this Phase 3 TRAILBLAZER-ALZ 2 study replicate and extend those from the Phase 2 TRAILBLAZER-ALZ study – Donanemab significantly slowed disease progression in individuals with early symptomatic AD
- Donanemab exhibited consistent efficacy across populations, across all cognitive and functional secondary endpoints, and across multiple analysis methods
- Although participants in the low-medium tau and combined populations had similar magnitude of responses from donanemab, effects were greater in the low-medium tau population. There may be a greater benefit from amyloid-lowering therapies when initiated at an earlier symptomatic disease stage
- The safety profile of donanemab was similar to that seen in TRAILBLAZER-ALZ and consistent with class effects observed with amyloid plaque-lowering therapies
- Donanemab reduced brain amyloid plaque, plasma P-tau217, and GFAP at the earliest post-baseline measured study timepoint (12 weeks for plasma and 24 weeks for PET); over 50% of trial participants achieved amyloid clearance at 52 weeks
- The observed benefit seen across populations, clinical outcomes and analytic approaches reinforces the promise of donanemab as a treatment for early symptomatic AD

Abbreviations: AD=Alzheimer's disease; GFAP=glial fibrillary acidic protein; PET=Positron Emission Tomography

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TRAILBLAZER-ALZ 2: Panel Discussion and Question/Answer Session

Craig Ritchie, Mark Mintun

Alzheimer's Association International Conference (AAIC)
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Donanemab in Early Symptomatic Alzheimer Disease

The TRAILBLAZER-ALZ 2 Randomized Clinical Trial

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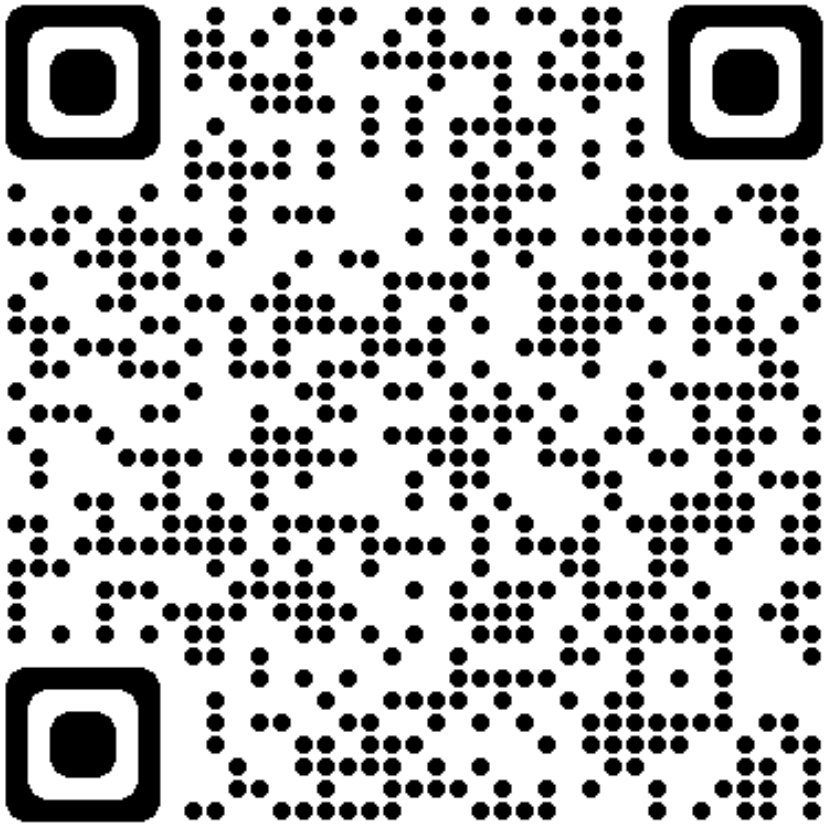

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