Donanemab in Early Symptomatic Alzheimer's Disease: Additional Insights from TRAILBLAZER-ALZ 2

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Clinical Trials on Alzheimer's Disease (CTAD) – 16th Annual Conference
Boston, Massachusetts, USA, and Online
October 24 - 27, 2023

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Disclosures

- Takeshi Iwatsubo reports receiving payment or honoraria from Eli Lilly and Company and Eisai for lectures, writing, or educational events.
- 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.

Acknowledgments

- We gratefully acknowledge the contribution and dedication of all the patients with AD, their families, and their caregivers who participated in this study, along with trial site investigators and personnel.
- We acknowledge contributions from Carmen Deveau, Paula Hauck, Staci Engle, and Sinead Ryan, the TRAILBLAZER-ALZ 2 study team, and vendor partners.
- This study was sponsored by Eli Lilly and Company.

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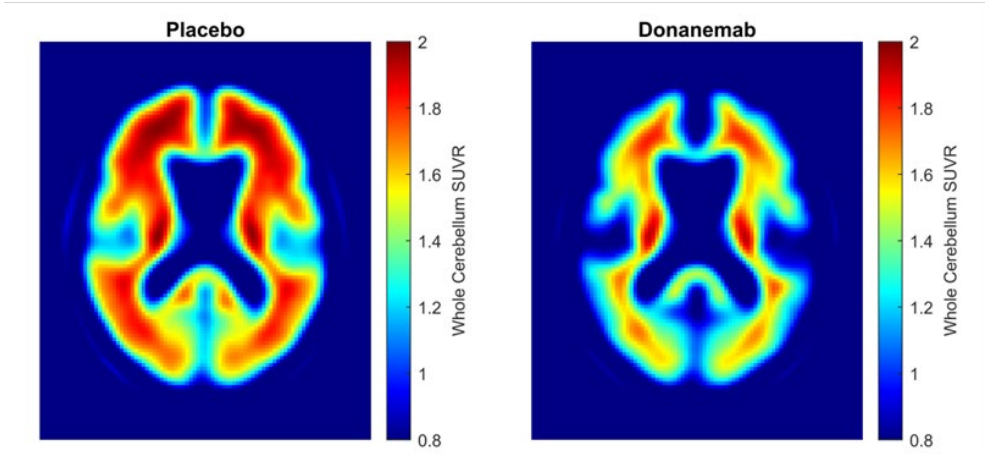
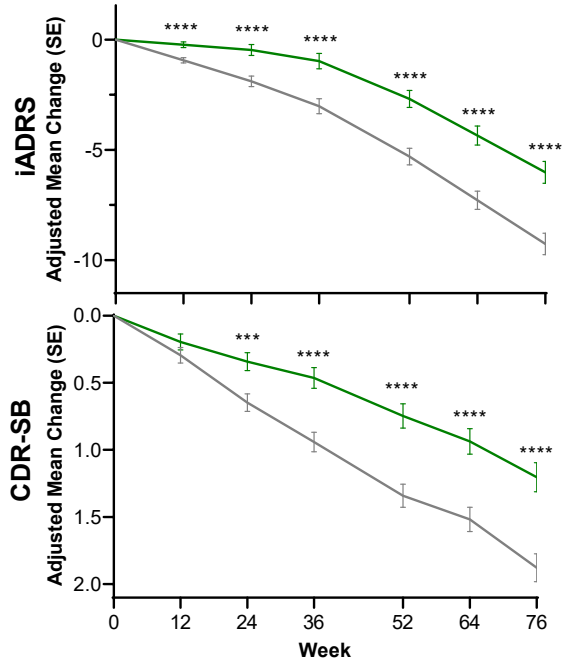
Today's Program

Presentation	Speaker
ARIA Insights from the Donanemab Trials	Steven M. Greenberg
Predicting Efficacy in Donanemab-Treated Participants	Mark Mintun
Clinical Relevance of Donanemab Treatment	Alireza Atri
Panel Discussion and Question/Answer Session	Takeshi Iwatsubo

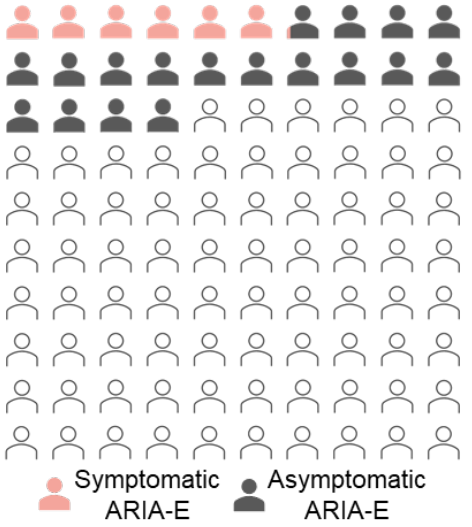
Summary of TRAILBLAZER-ALZ 2 key results



- Donanemab treatment reduced amyloid plaque by **87 Centiloids** in 76 weeks.
- **69%** of participants cleared amyloid and switched from donanemab to placebo by 76 weeks.



- Donanemab slowed progression on the iADRS by **35%** and on CDR-SB by **36%** at 76 weeks in the low-medium tau population.



- ARIA-E was the most common side-effect, (**24%** of donanemab-treated participants).
- Three deaths from ARIA-related complications occurred.

[1] Sims JR et al. JAMA. 2023 doi: 10.1001/jama.2023.13239.
Abbreviations: ARIA-E=amyloid-related imaging abnormalities-edema/effusions; iADRS= integrated Alzheimer's Disease Rating Scale; CDR-SB=Clinical Dementia Rating-Sum of Boxes.
*** P<0.001, **** P<0.0001

ARIA Insights From Donanemab Trials

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TRAILBLAZER-ALZ 2 & Addendum

TRAILBLAZER-ALZ 2

A multicenter, randomized, double-blind, placebo-controlled, 18-month Phase 3 trial that enrolled 1736 participants with early symptomatic Alzheimer's disease with amyloid and tau pathology confirmation via PET scan.

Addendum, additional N=1053

- Open-label donanemab treatment
- Enrolled by amyloid pathology as only neuropathological criterion, including participants with **lower amyloid** and **no/very low tau**
- Safety and biomarker assessments

ARIA in donanemab-exposed participants

Larger participant populations with lower amyloid and tau levels will expand current understanding of ARIA in individuals who received donanemab.

Risk factors of ARIA

The genetic *APOE* ε4 allele increases the risk of ARIA[1]. Machine learning approaches can facilitate identification or generate hypotheses for further variables to evaluate, such as baseline characteristics, comorbidities, and concomitant medications that may be associated with ARIA risk[2].

[1] Sims JR et al. JAMA. 2023 doi: 10.1001/jama.2023.13239.
[2] Sperling R. Lancet Neurol. 2012 doi: 10.1016/S1474-4422(12)70015-7.
Abbreviations: *APOE*=apolipoprotein E; ARIA=amyloid-related imaging abnormalities; PET=Positron Emission Tomography.

Baseline Demographics and Disease Characteristics

	TRAILBLAZER-ALZ[a]	TRAILBLAZER-ALZ 2	Addendum
Demographics in donanemab-treated	(N=131)	(N=860)	(N=1053)
Sex, n (%) female	68 (51.9)	493 (57.3)	566 (53.8)
Age, mean (SD), in years	75.0 (5.6)	73.0 (6.2)	74.6 (5.9)
Race n (%)			
Asian	1 (0.8)	57 (6.6)	64 (6.1)
Black or African American	5 (3.8)	19 (2.2)	37 (3.5)
White	122 (93.1)	781 (90.9)	940 (89.7)
American Indian or Alaska Native	2 (1.5)	2 (0.2)	2 (0.2)
Multiple	1 (0.8)	0	4 (0.4)
Ethnicity[b], n (%) Hispanic/Latino	**5 (3.8)**	**35 (5.7)**	**100 (11.0)**
***APOE* ε4 carrier, n (%)**	95 (72.5)	598 (69.8)	652 (62.4)
ε4 homozygous	25 (19.1)	143 (16.7)	114 (10.9)
Screening amyloid Centiloids, mean (SD)	**107.6 (36.0)**	**103.5 (34.5)**	**82.5 (37.2)**
Screening MMSE by clinical category			
Mild cognitive impairment (≥27)	**24 (18.3)**	**146 (17.0)**	**345 (32.8)**
Mild AD (20-26)	88 (67.2)	713 (82.9)	707 (67.1)
Moderate AD (<20)	0	1 (0.1)	1 (0.1)

Numbers of participants with non-missing data were used as denominators to calculate percentages.
[a]Phase 2 trial investigating safety and efficacy of donanemab, NCT03367403.
[b]Ethnicity reporting was limited to participants in the United States/Puerto Rico only.

Abbreviations: AD=Alzheimer's disease; *APOE*=apolipoprotein E; MMSE=Mini-Mental State Examination; N=total number of participants; n=number of participants per category; SD=standard deviation.

ARIA and Macrohemorrhage

	TRAILBLAZER-ALZ	TRAILBLAZER-ALZ 2	Addendum	Total
Event[a], n (%) in donanemab-treated	(N=131)	(N=853)	(N=1047)	(N=2031)
Any ARIA (-E or -H)	51 (38.9)	314 (36.8)	335 (32.0)	700 (34.5)
ARIA-E	**36 (27.5)**	**205 (24.0)**	**207 (19.8)**	**448 (22.1)**
Symptomatic	8 (6.1)	52 (6.1)	42 (4.0)	102 (5.0)
SAE of ARIA-E	2 (1.5)	13 (1.5)	7 (0.7)	22 (1.1)
ARIA-H	40 (**30.5**)	268 (**31.4**)	285 (**27.2**)	593 (**29.2**)
SAE of ARIA-H	0	4 (0.5)	3 (0.3)	7 (0.3)
Macrohemorrhage	0	3 (0.4)	4 (0.4)	7 (0.3)
SAE of macrohemorrhage	0	1 (0.1)	2 (0.2)	3 (0.1)

[a]ARIA and macrohemorrhage events based on MRI or TEAE cluster.
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.

Testing ARIA-E Association with 42 Baseline Variables

Associations with ARIA-E were identified in a post-hoc analysis using machine learning approaches, which incorporated penalized regression and decision tree-based modeling.

Demographic

Age
Sex
Race
Body weight
Yrs diagnosed

Genetic

APOE ε4
BIN1

Amyloid/Tau PET

Tau PET SUVR
Amyloid PET Centiloid

Clinical

MMSE
CDR−SB

MRI/vMRI

of microhemorrhages
Presence of cortical superficial siderosis
Level of white matter disease
Infarct (stroke, cortical, lacunar, other)
Whole cortex volume
Ventricle volume
Hippocampal volume

Blood Pressure

Diastolic blood pressure
Systolic blood pressure
Mean arterial pressure

Blood Analytes

P-tau217
P-tau181
NFL
GFAP
CRP
WBC
Platelets
Monocytes
Lymphocytes

Concomitant Meds

Antidepressants
Antihypertensives
Statins
Arthritic/Osteoarthritic
Diabetes
Antithrombotics

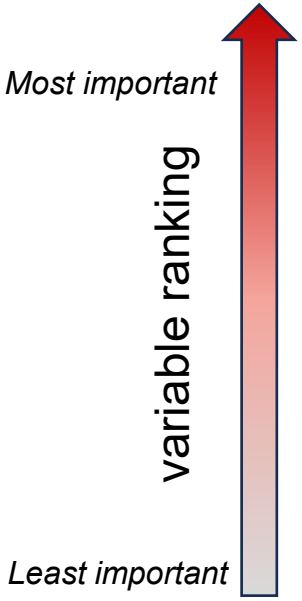
Comorbidities

Hypertension
Depression
Myocardial infarction
Diabetes
Stroke
Dyslipidemia

C_2N plasma P-tau217 and Quanterix Simoa® GFAP, NFL and P-tau181 assays. Abbreviations: *APOE*=apolipoprotein E; ARIA-E=amyloid-related imaging abnormalities-edema/effusions; BIN1=bridging integrator-1; CDR−SB=clinical dementia rating scale−sum of boxes; CRP=c-reactive protein; GFAP=glial fibrillary acidic protein; (v)MRI=(volumetric) magnetic resonance imaging; MMSE=mini-mental state examination; NFL=neurofilament light chain; PET=positron emission tomography; SUVR=standard uptake value ratio; WBC=white blood cells; Yrs=years.

ARIA-E Risk Factors: Factor Evaluation

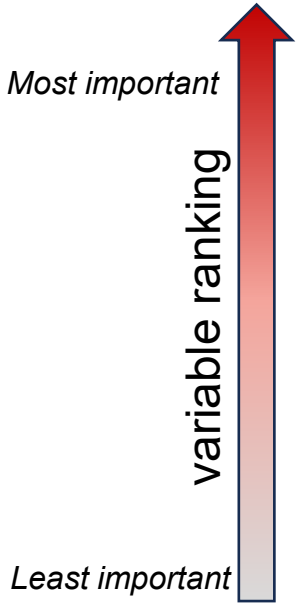
42 baseline variables → **Univariate Analysis**
12 variables identified



↑*ARIA association*	↓*ARIA association*
***APOE* ε4**	**Antihypertensives**
# of microhemorrhages	**↑ White blood cells**
Presence of cortical superficial siderosis	**History of myocardial infarction**
Amyloid PET Centiloid	**History of hypertension**
Diastolic blood pressure	**↑ Age**
Mean arterial pressure	**Diabetes medications**

Logistic regression was applied and variables with FDR adjusted p-value <0.1 are listed.

42 baseline variables → **Machine Learning**
6 variables identified



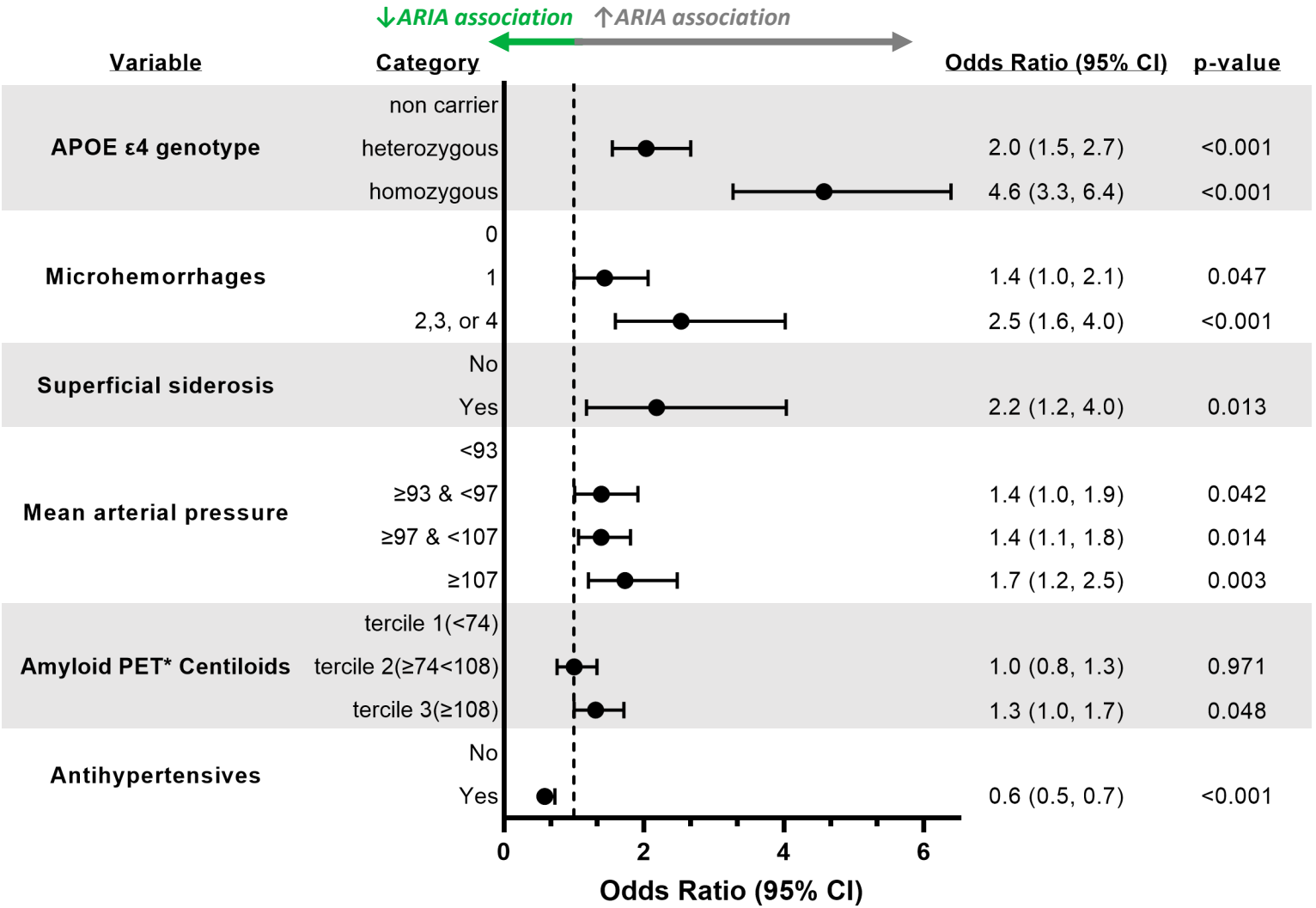
↑*ARIA association*	↓*ARIA association*
***APOE* ε4**	**Antihypertensives**
# of microhemorrhages	
Presence of cortical superficial siderosis	
Amyloid PET Centiloid	
Mean arterial pressure	

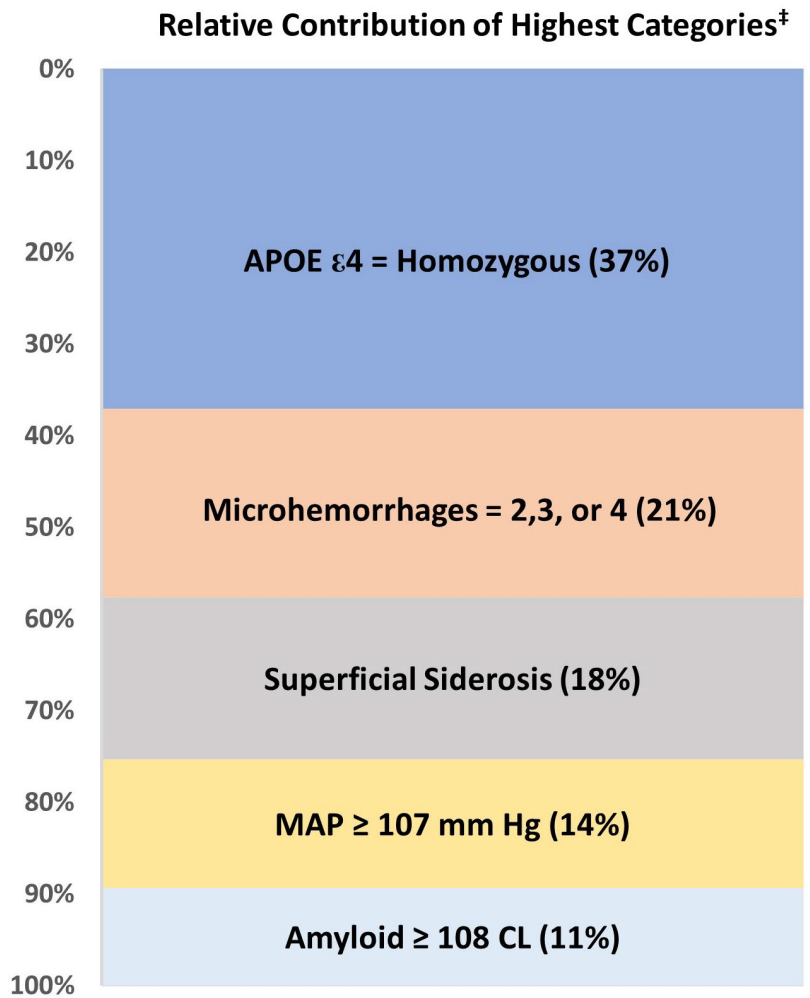
Machine-learning models

- LASSO shrinks less relevant variables to zero using regularization, reducing false-positive discoveries.
- Ensemble tree-based models combine multiple trees to mitigate false positives.
- Both approaches were applied, and 6 variables were selected.

Abbreviations: *APOE*=apolipoprotein E; ARIA=amyloid-related imaging abnormalities; FDR=false discovery rate; LASSO=least absolute shrinkage and selection operator; PET=positron emission tomography.

Key Baseline Factors Associated With ARIA-E†

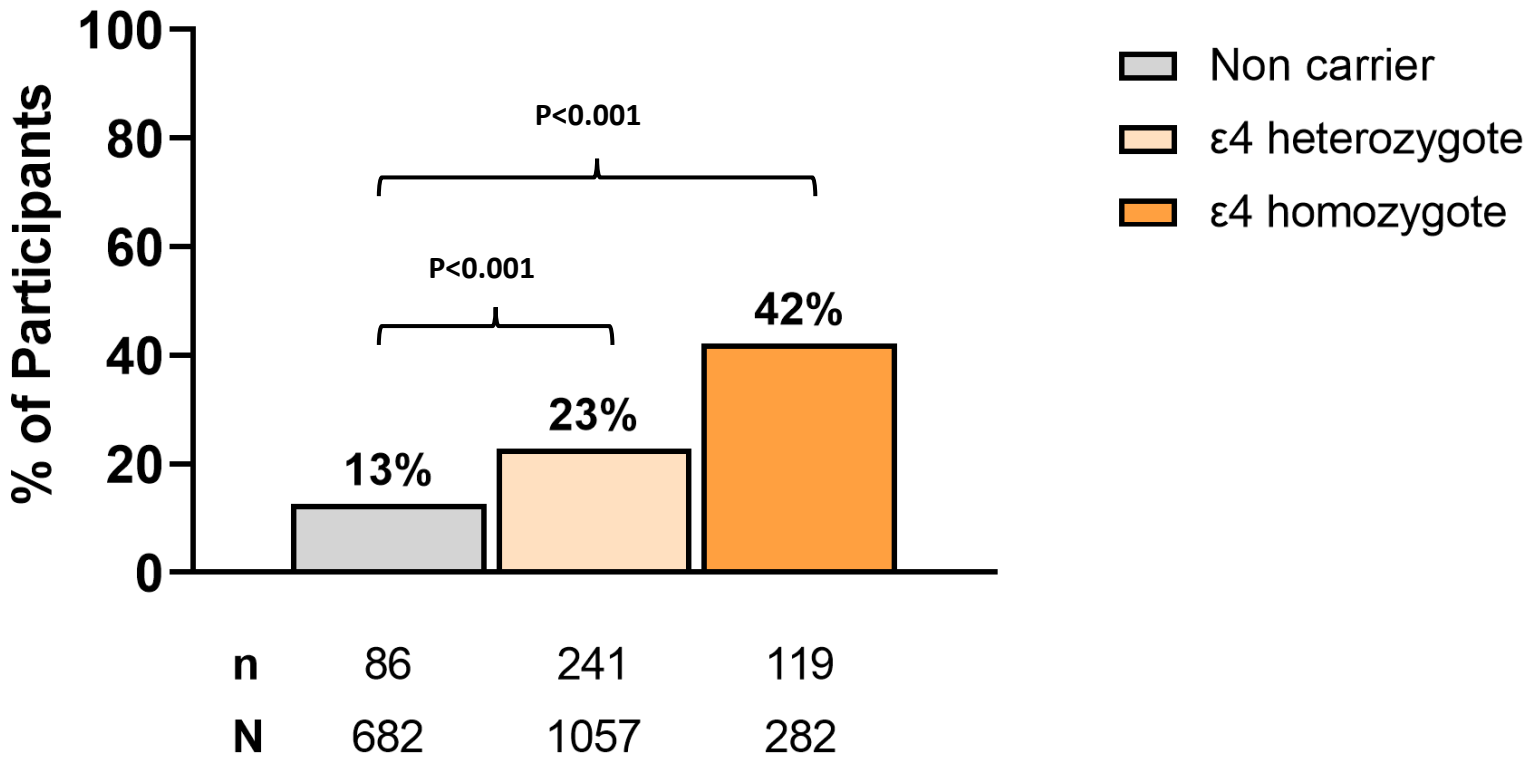




Total sample size N=2021; With ARIA-E n=446. †Analyses completed with multivariate logistic regression using TRAILBLAZER-ALZ, TRAILBLAZER-ALZ 2, and Addendum populations. *Cerebellum used as reference region. ‡Pseudo R-square=7.44%.
Abbreviations: *APOE*=apolipoprotein E; ARIA-E=amyloid-related imaging abnormalities-edema/effusions; CI=confidence interval; CL=Centiloids; mm Hg=millimeter of mercury; MAP=mean arterial pressure; PET=positron emission tomography.

ARIA-E in Participants by Genotype

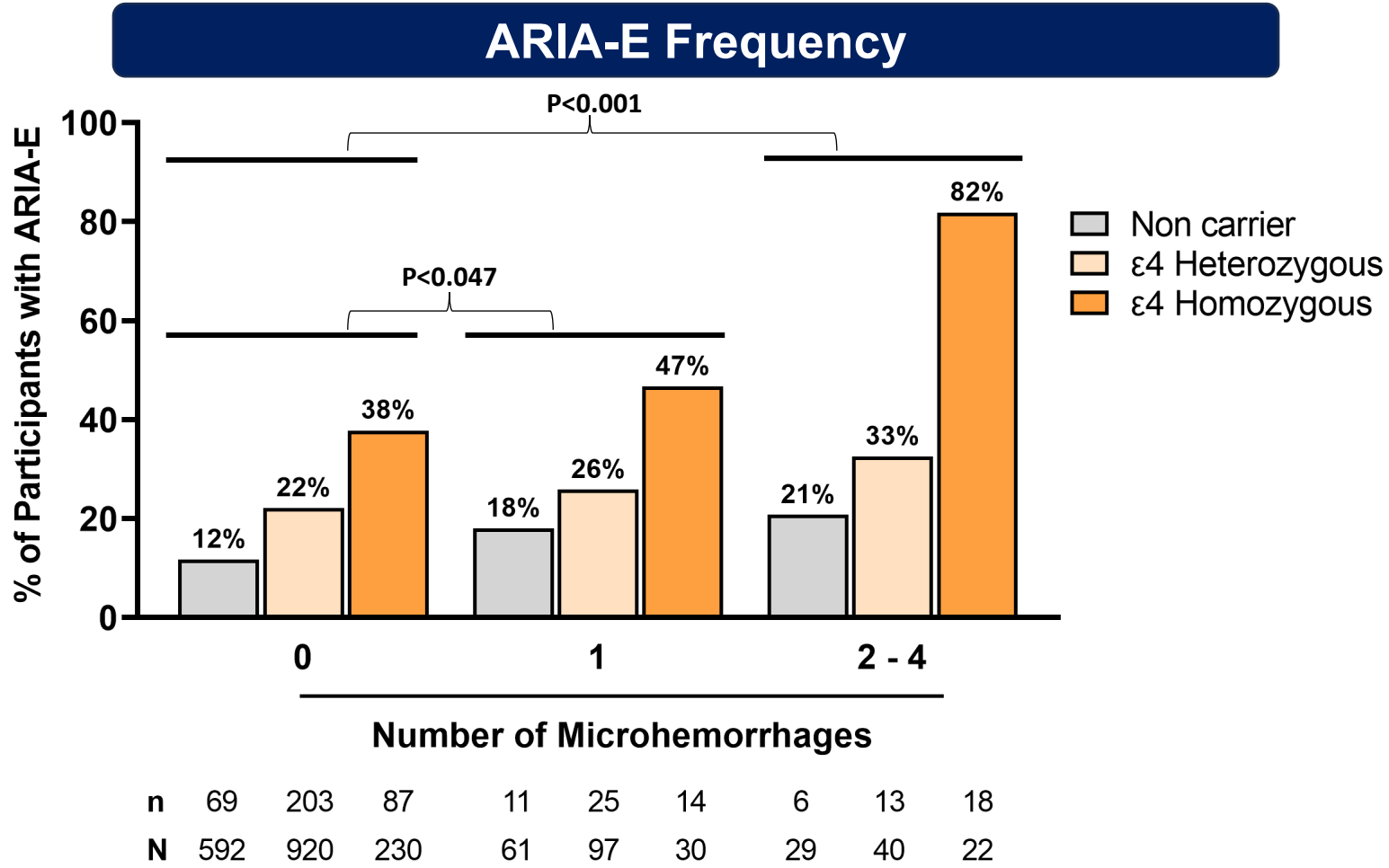
ARIA-E Frequency



ARIA-E frequency increases across *APOE* ε4 genetic type, consistent with other amyloid-targeting agents.

Multivariate logistic analysis based on 10-fold cross-validation using the combined data.
Abbreviations: *APOE*=apolipoprotein E; ARIA-E=amyloid-related imaging abnormalities−edema and effusions; N=total number of participants; n=number of participants per category; P=p-value.

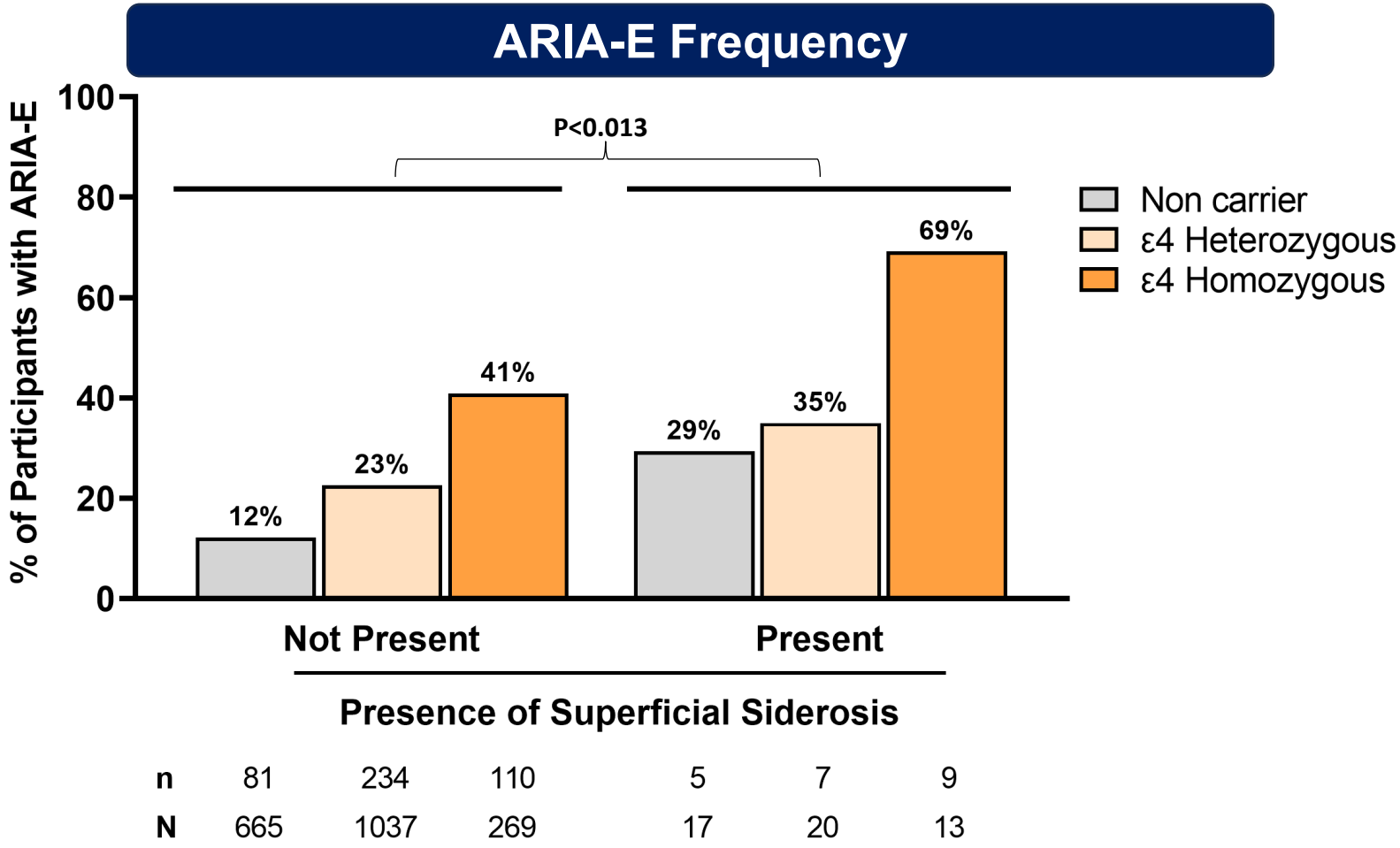
ARIA-E in Participants with Baseline Microhemorrhages



ARIA-E frequency increases within *APOE* ε4 genotype and number of microhemorrhages.

Multivariate logistic analysis based on 10-fold cross-validation using the combined data.
Abbreviations: *APOE*=apolipoprotein E; ARIA-E=amyloid-related imaging abnormalities−edema and effusions; N=total number of participants; n=number of participants per category; P=p-value.

ARIA-E in Participants with Baseline Superficial Siderosis

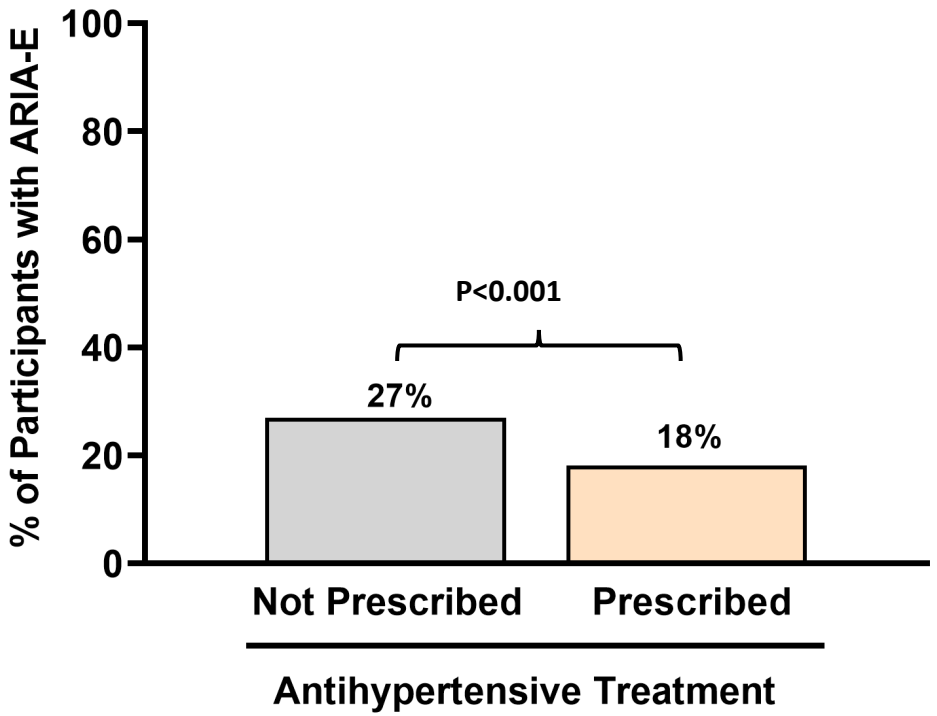


ARIA-E frequency increases within *APOE* ε genotypes with the presence of baseline superficial siderosis.

Multivariate logistic analysis based on 10-fold cross-validation using the combined data.
Abbreviations: *APOE*=apolipoprotein E; ARIA-E=amyloid-related imaging abnormalities-edema/effusions; N=total number of participants; n=number of participants per category; P=p-value.

ARIA-E in Participants With Baseline Antihypertensive Medication use

ARIA-E Frequency

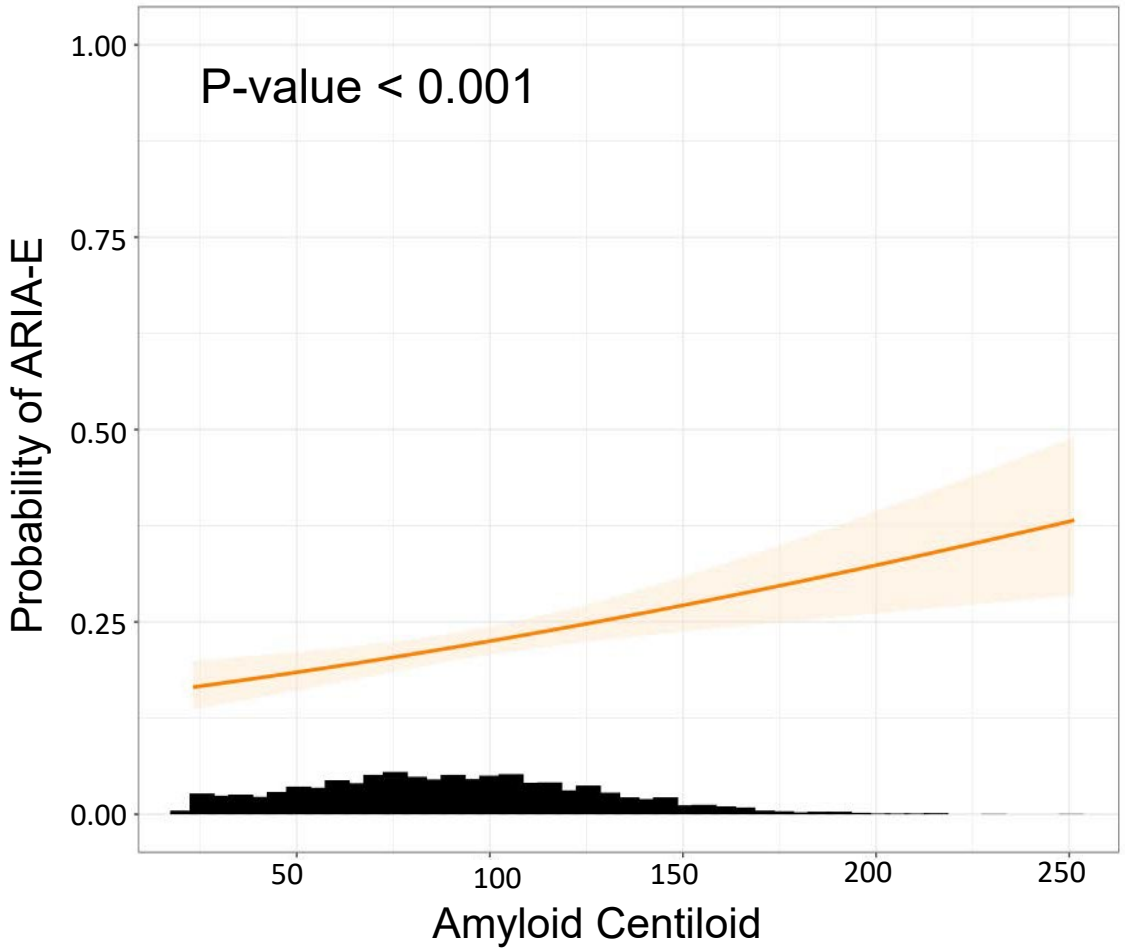


	Not Prescribed	Prescribed
n	245	201
N	909	1112

ARIA-E frequency decreases with use of antihypertensive medications.

Multivariate logistic analysis based on 10-fold cross-validation using the combined data.
Abbreviations: ARIA-E=amyloid-related imaging abnormalities-edema/effusions; N=total number of participants; n=number of participants per category; P=p-value.

Association of ARIA-E with Baseline Amyloid Centiloid



The probability of ARIA-E was estimated using univariate logistic regression modeling and included baseline amyloid Centiloid as a covariate.
Abbreviations: ARIA-E=amyloid-related imaging abnormalities-edema/effusions.

Conclusions

- ARIA-E frequency was assessed across 2031 donanemab exposures in populations with concomitant medications and comorbid conditions representative of the US Alzheimer's disease Medicare population.[1,2]
- Machine-learning approaches suggest 6 independent baseline variables associated with ARIA-E frequency: *APOE* ε4 genotype, number of microhemorrhages, superficial siderosis, mean arterial pressure, amyloid PET Centiloids, and antihypertensive medication use.
- ARIA-E frequency increases within & across *APOE* ε4 genotype with presence and increase in baseline microhemorrhages and/or presence of superficial siderosis.
- Predominant ARIA risk factors are consistent with pre-existing cerebral amyloid angiopathy.
- These post-hoc exploratory analyses are hypothesis-generating for future work in validation across amyloid-targeting therapies and may yield modifiable factors.

1 Schroeder et al. Characterize demographics, comorbidities and co-medications in newly diagnosed United States (US) Alzheimer's Disease patients using Medicare claims AAIC. 2023.
2 Publication submitted.
Abbreviations: *APOE*=apolipoprotein E; ARIA-E=amyloid-related imaging abnormalities-edema/effusions

Predicting Efficacy in Donanemab-Treated Participants

Mark A. Mintun, Lars L. Raket, Jennifer A. Zimmer, Cynthia D. Evans, Ming Lu, JonDavid Sparks, Emily C. Collins, Sergey Shcherbinin, Hong Wang, Emel Serap Monkul, Lei Shen, Dawn A. Brooks, John R. Sims

Eli Lilly and Company, Indianapolis, USA

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Presenter's Disclosure

- Mark Mintun is Senior Vice President of Neuroscience R&D in Eli Lilly and Company and President of Avid Radiopharmaceuticals, a wholly owned subsidiary 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 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.
- Eli Lilly and Company has pending patent application(s) on a P-tau217 blood test.
- All discussions refer to investigational purposes only.

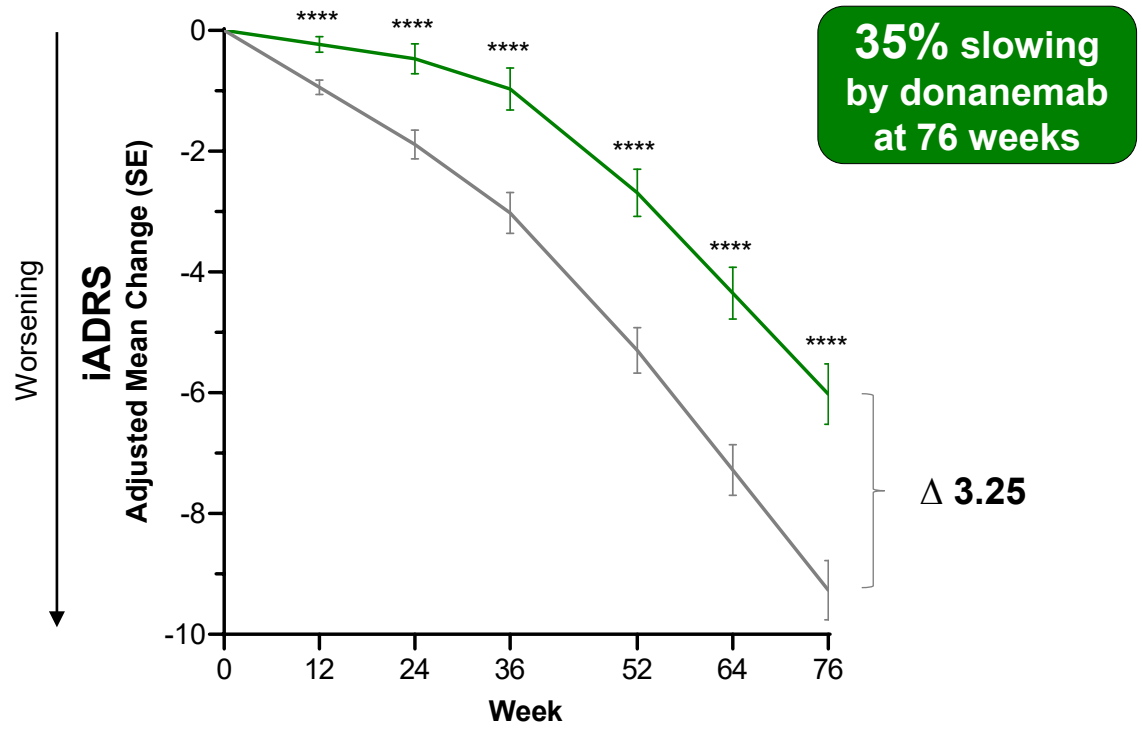
Identifying factors associated with efficacy of donanemab

Results from TRAILBLAZER-ALZ 2 suggested that donanemab treatment slowed relative disease progression to a greater degree in participants with less advanced disease. To further investigate this hypothesis, post-hoc analyses were conducted to explore:

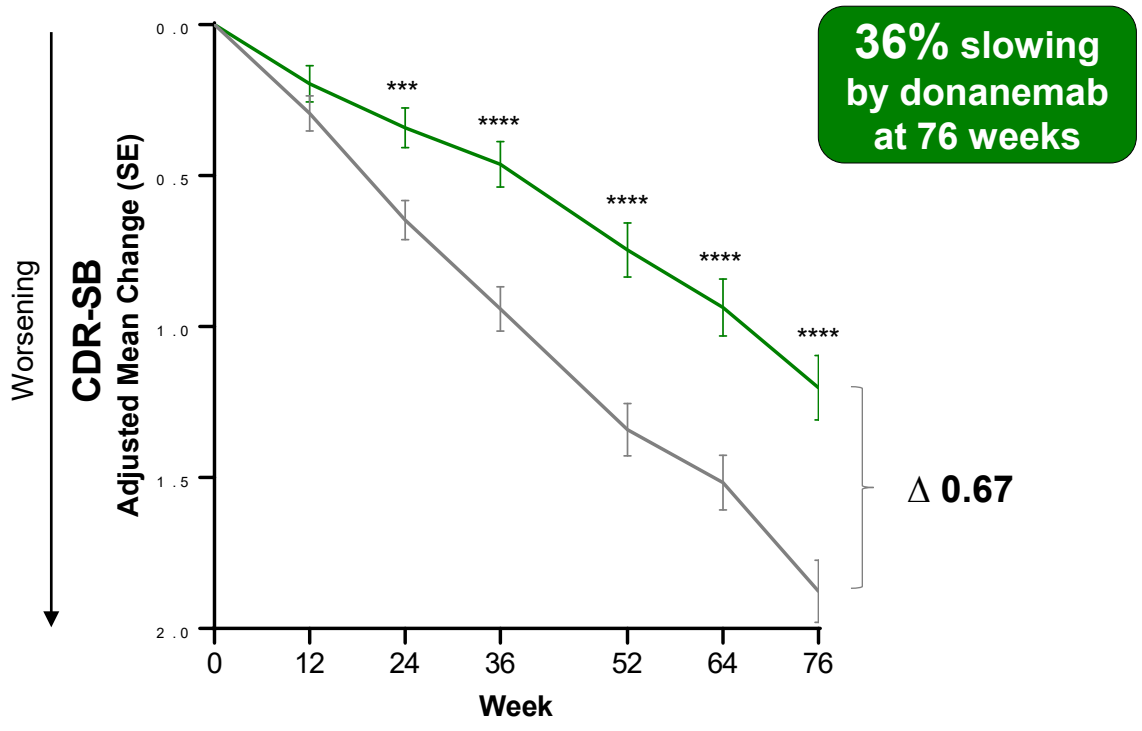
- Slowing of clinical decline according to baseline tau PET
- Biomarkers of efficacy in no/very low tau participants from the recent TRAILBLAZER-ALZ 2 open label addendum
- Effects of additional baseline characteristics as predictors of donanemab treatment benefit (P-tau217, age, and disease stage)

TRAILBLAZER-ALZ 2 Phase 3 Primary and Secondary Outcomes: iADRS and CDR-SB

iADRS: Low-medium Tau Population

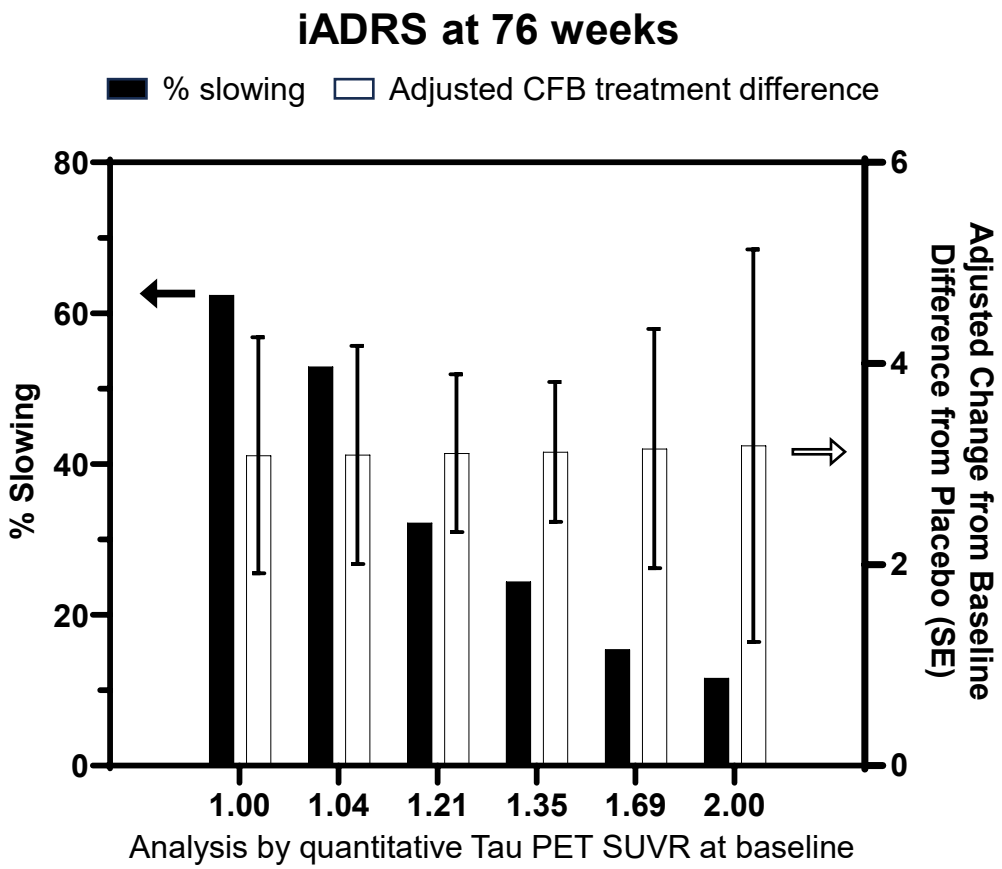


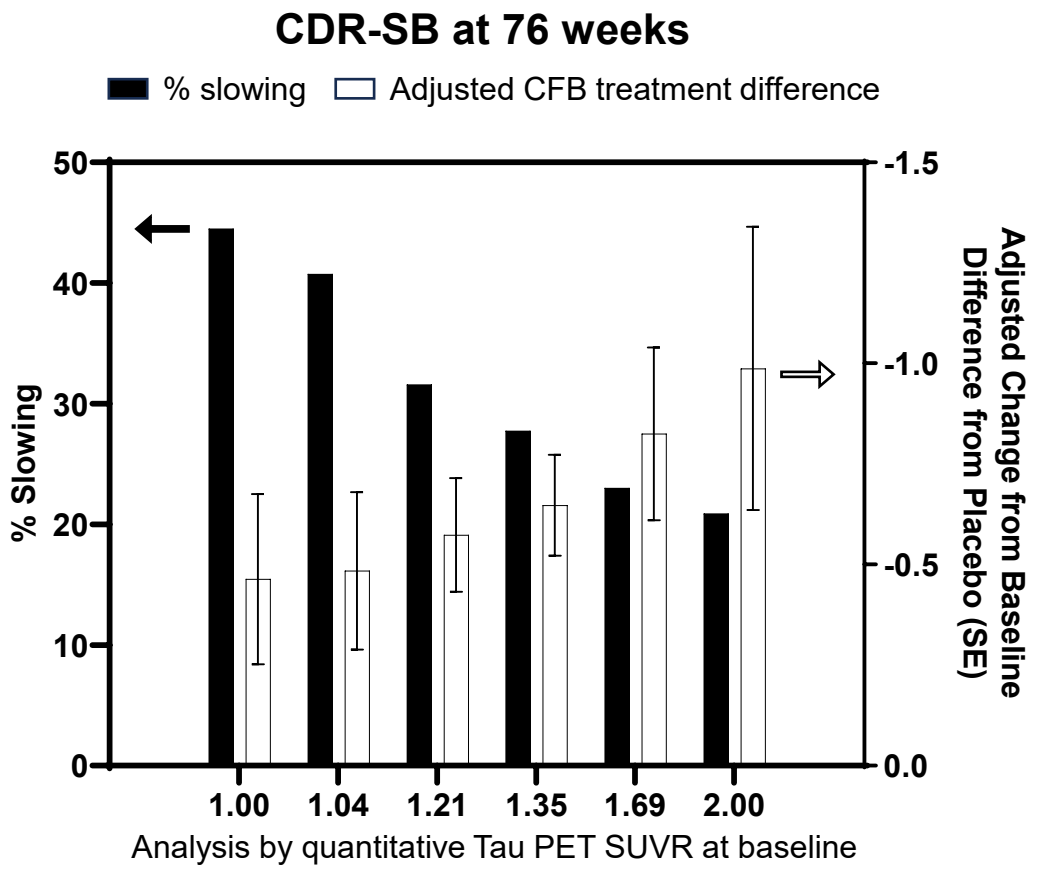
CDR-SB: Low-medium Tau Population



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, 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<0.001, **** P<0.0001. Abbreviations: CDR-SB=Clinical Dementia Rating–Sum of Boxes; iADRS=Integrated Alzheimer's Disease Rating Scale; n=number of participants; NCS=natural cubic spline; SE=Standard Error

Model of MMRM analysis using tau SUVr interaction predicts greater percent slowing of clinical decline with lower baseline tau



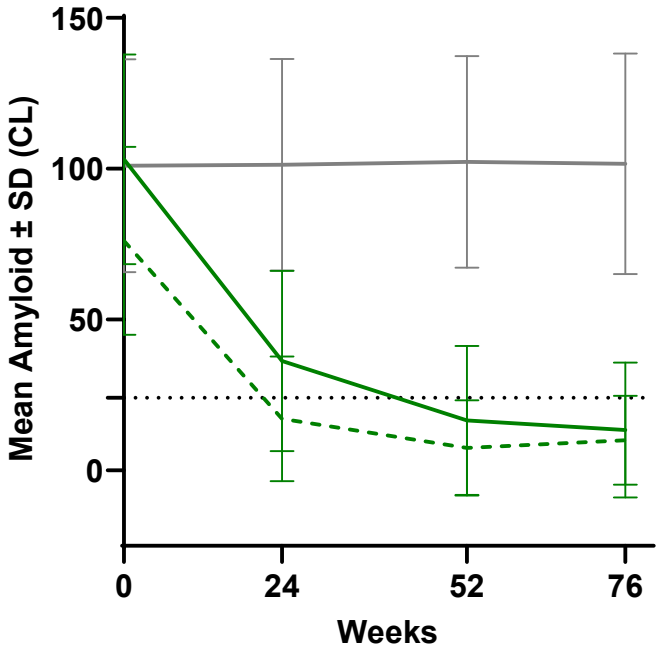


Despite smaller percent slowing, significant change from baseline differences from placebo are observed across baseline tau PET levels

Mixed model repeated measures methodology that includes fixed factors for treatment, visit, treatment-by-visit interaction, and covariates for baseline score, baseline score-by-visit interaction, age at baseline, baseline tau category, pooled investigator, baseline AchI/Memantine use, baseline tau (AD signature-weighted neocortical SUVr), baseline tau-by-visit, baseline tau-by-treatment and baseline tau-by-treatment-by-visit interaction. Models allow for the estimation of adjusted mean differences between treatment arm at each visit, by various tau SUVr levels. Modeled data uses combined population SUVR only (no visual interpretation). Abbreviations: AD=Alzheimer's Disease; CFB=change from baseline; CDR-SB=Clinical Dementia Rating-Sum of Boxes; iADRS=Integrated Alzheimer's Disease Rating Scale; SE=Standard Error.

What are donanemab-mediated biomarker responses in participants with “no tau”?

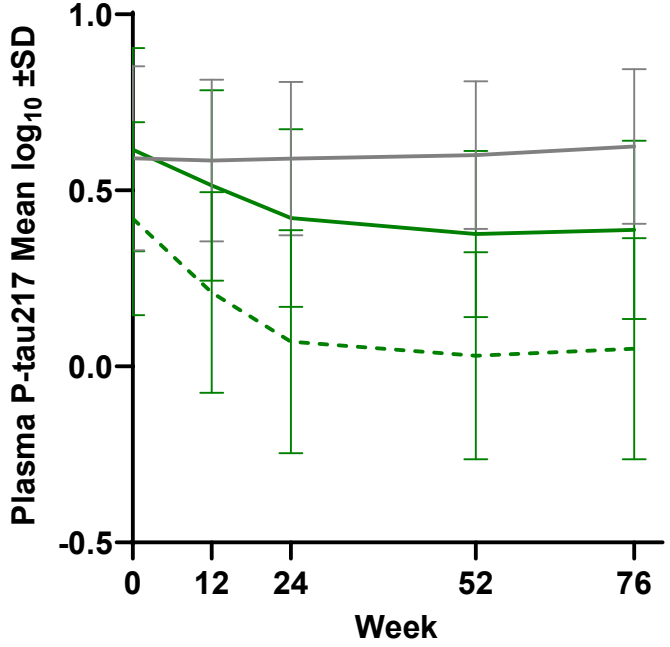
Amyloid plaque



Population; N (% reduction from baseline) at 76 weeks

- TB2 Placebo - Low/Medium tau; N=470 (-1%)
- TB2 Donanemab - Low/Medium tau; N=433 (87%)
- TB2 Addendum Donanemab - No tau; N=203 (87%)

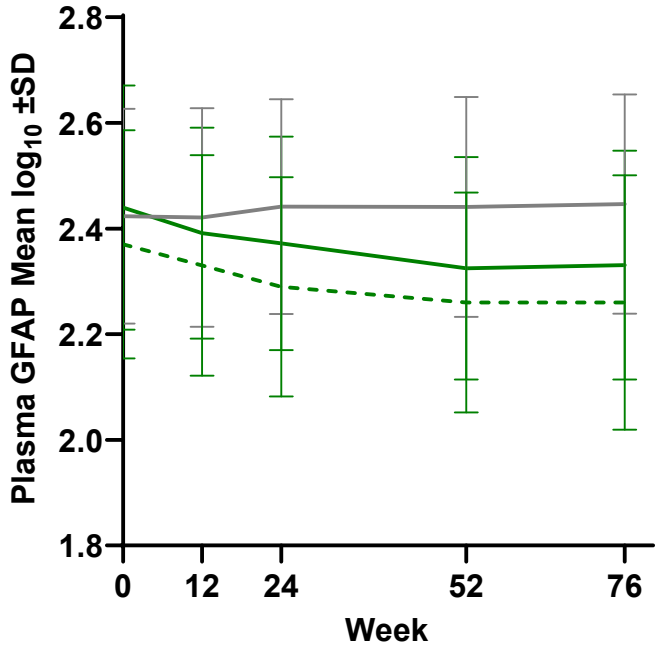
Plasma P-tau217



Population; N (% reduction from baseline) at 76 weeks

- TB2 Placebo - Low/Medium Tau; N=429 (-8%)
- TB2 Donanemab - Low/Medium Tau; N=395 (41%)
- TB2 Addendum Donanemab - No tau; N=195 (57%)

GFAP

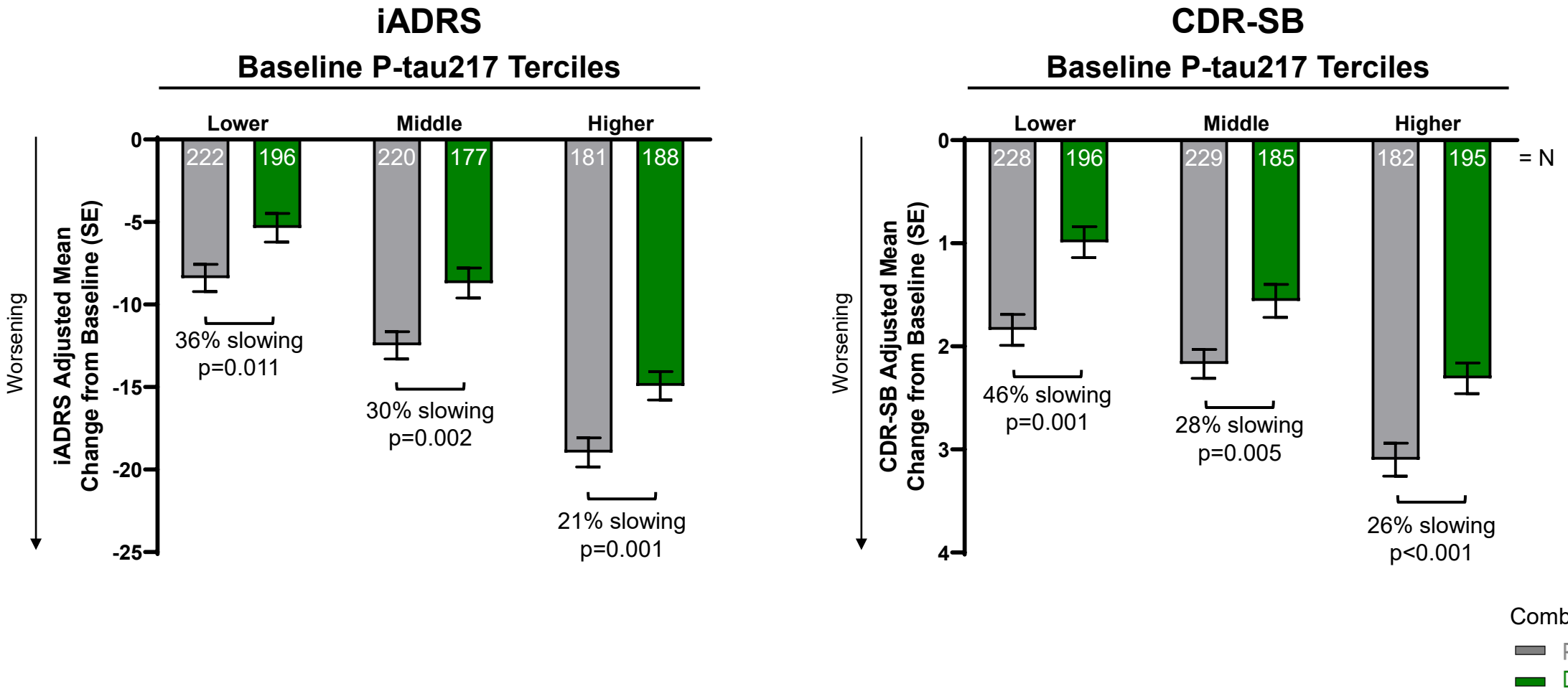


Population; N (% reduction from baseline) at 76 weeks

- TB2 Placebo Low/Medium Tau; N=451 (-6%)
- TB2 Donanemab Low/Medium Tau; N=417 (22%)
- TB2 Addendum Donanemab No tau; N=198 (22%)

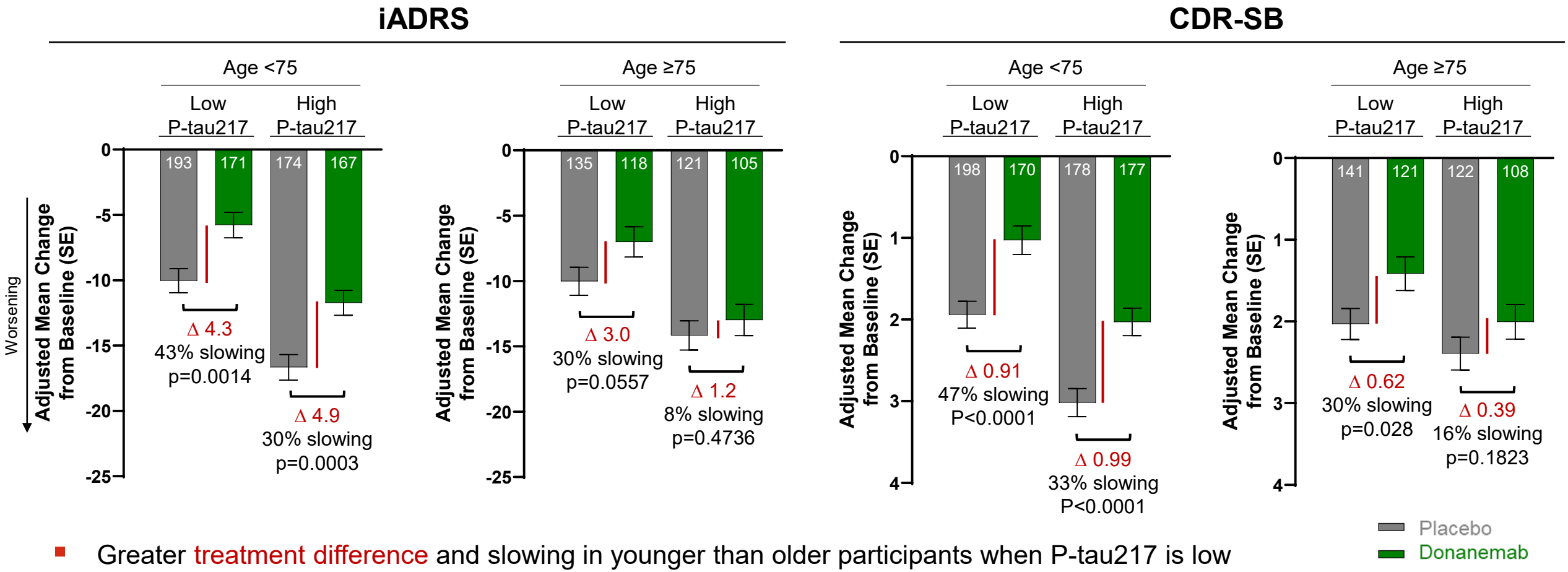
“No tau” (insufficient tau for TRAILBLAZER-ALZ 2 inclusion) based on visual and quantitative method (Mintun et al, N Engl J Med 2021). Data shown are not adjusted by modelling methodology. C_2N plasma P-tau217 and Quanterix Simoa® GFAP assays. Abbreviations: GFAP=Glial fibrillary acidic protein; N=number of participants; SD=Standard deviation.

Lower baseline P-tau217 is associated with greater slowing of clinical decline at 76 weeks



Adjusted 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. TRAILBLAZER-ALZ 2 Combined population. P-values are nominal. Abbreviations: CDR-SB=Clinical Dementia Rating – Sum of Boxes; iADRS=Integrated Alzheimer's Disease Rating Scale; N=number of participants; SE=Standard Error.

Age and P-tau217 effects on clinical decline (overall population)



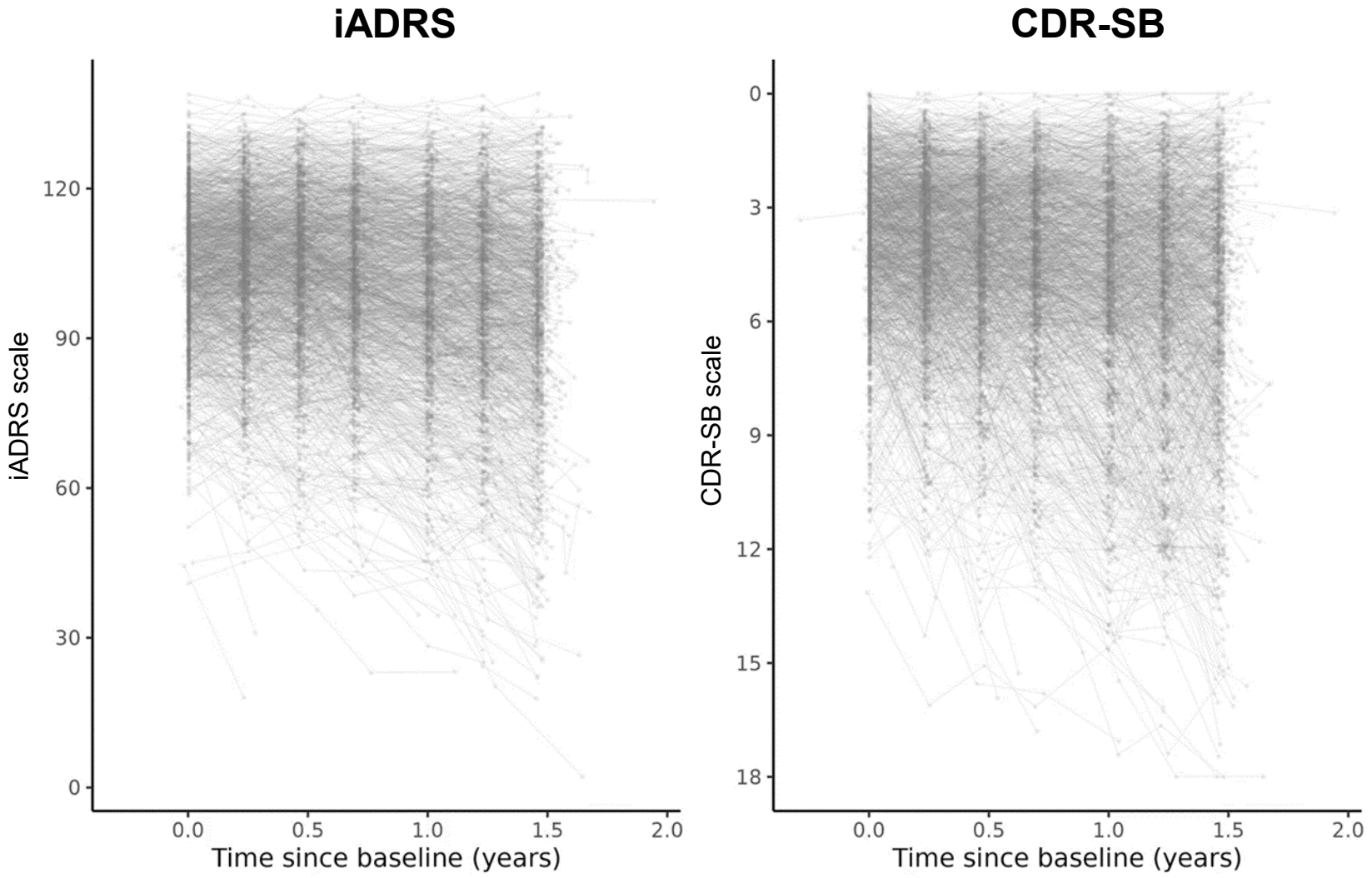
- Greater treatment difference and slowing in younger than older participants when P-tau217 is low
  - but the difference is greater in when P-tau217 is high
- Treatment difference for < 75 is similar in low and high P-tau groups, but the low P-tau group has greater slowing
- Treatment difference and slowing for ≥75 is greater in low P-tau than high P-tau in participants

Adjusted mean change from baseline (with participant number indicated along X-axis), SE, 95% CI and p-value are derived using mixed model repeated measures methodology with fixed factors for treatment, visit, subgroup, treatment-by-visit, treatment-by-subgroup, subgroup-by-visit, treatment-by-visit-by-subgroup interactions and covariates for baseline score, baseline score-by-visit interaction, baseline tau category, pooled investigator, baseline acetylcholinesterase inhibitor/memantine use.

Modeling disease stage in TRAILBLAZER-ALZ 2 based on clinical scale trajectories

Finding structure in trajectories of decline

- Estimated disease timeline based on longitudinal trajectories[1]
- Every patient had a latent disease time parameter that describes where they are on the disease trajectories



[1] Kühnel et al, Statistics in Medicine 2021

In illustrations, noise was added to patient-level scores to minimizing overplotting

Modeling disease stage in TRAILBLAZER-ALZ 2 based on clinical scale trajectories

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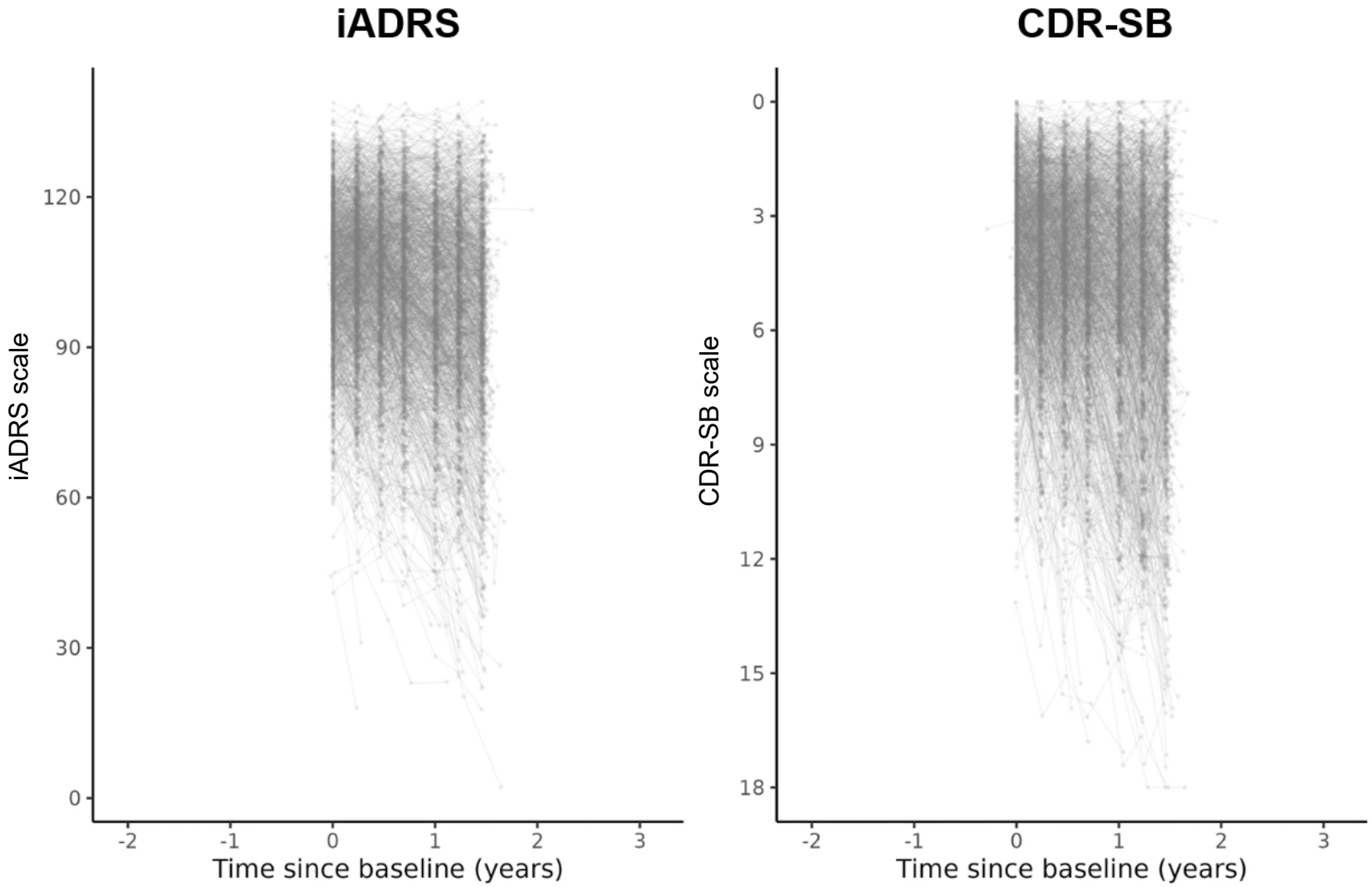

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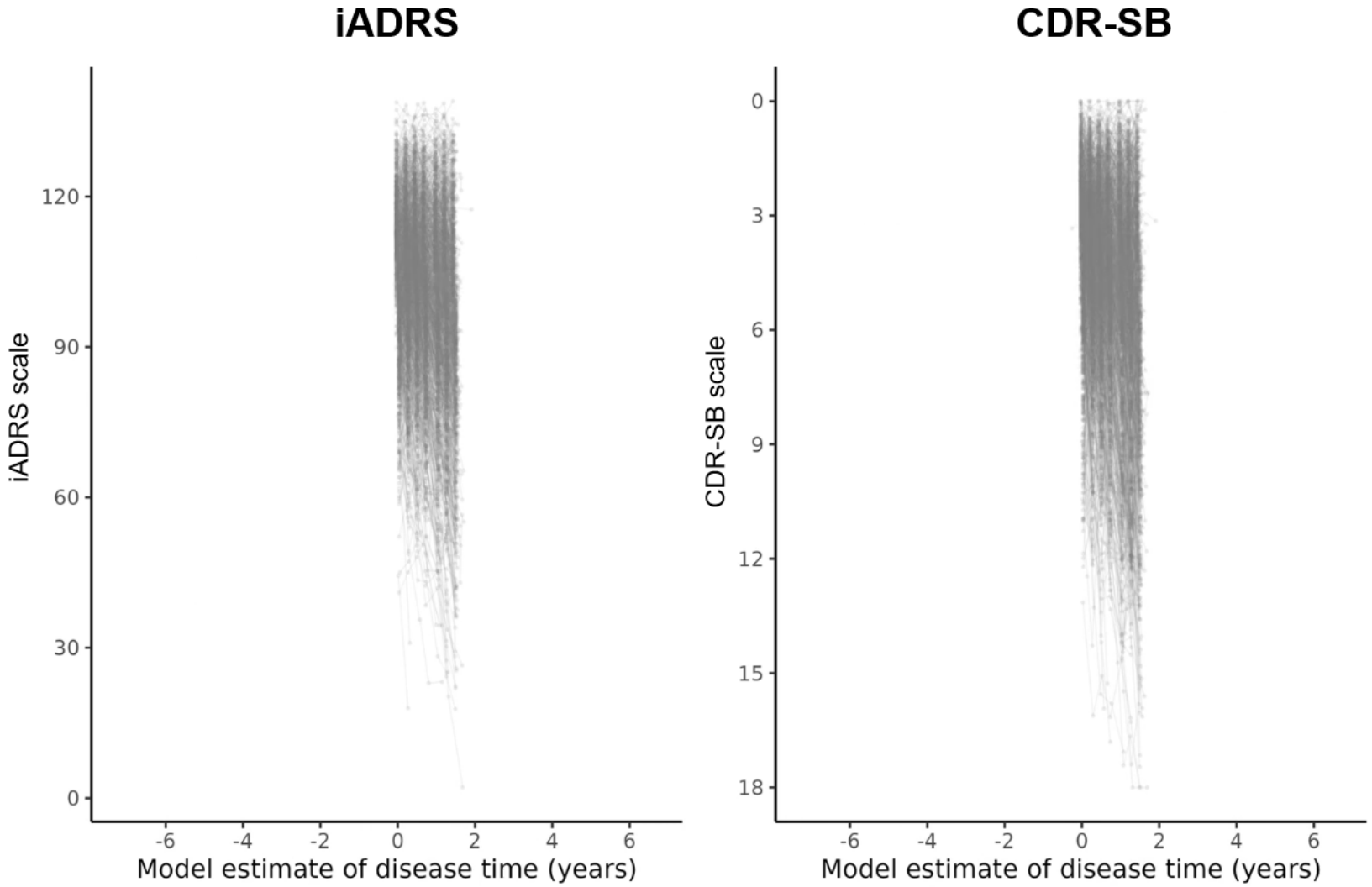

[1] Kühnel et al, Statistics in Medicine 2021

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Modeling disease stage in TRAILBLAZER-ALZ 2 based on clinical scale trajectories

Finding structure in trajectories of decline

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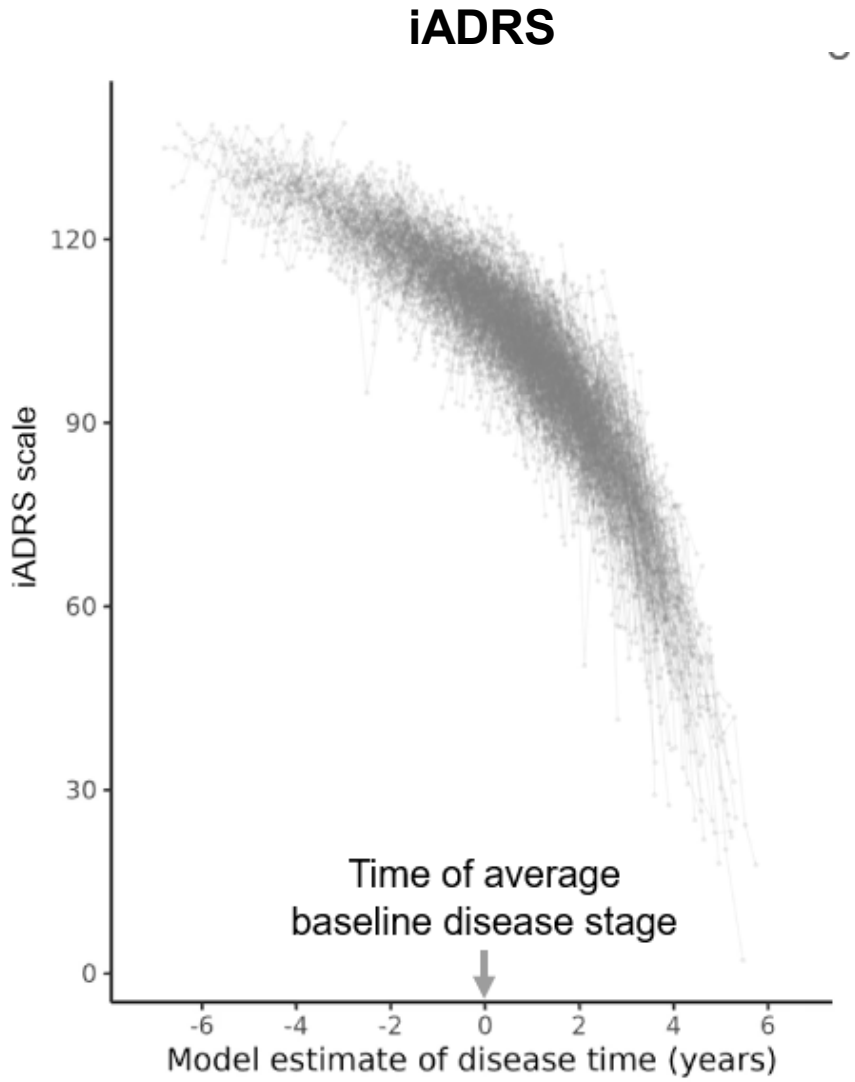

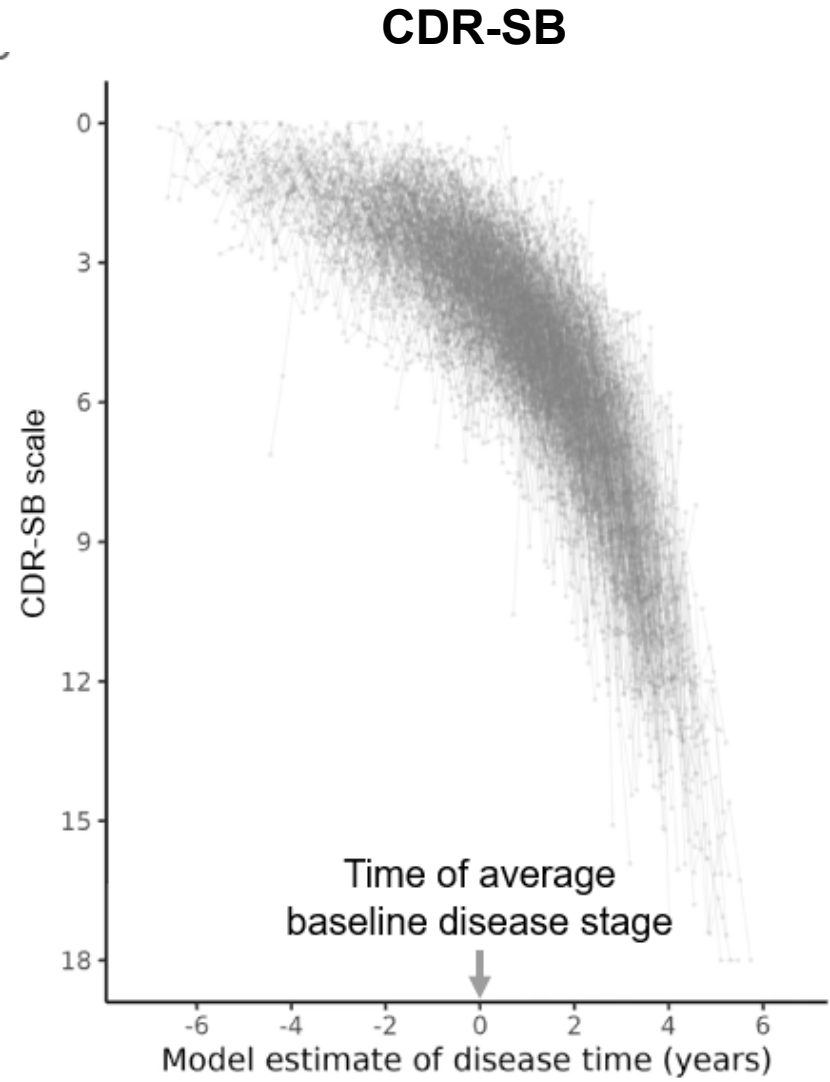

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Modeling disease stage in TRAILBLAZER-ALZ 2 based on clinical scale trajectories

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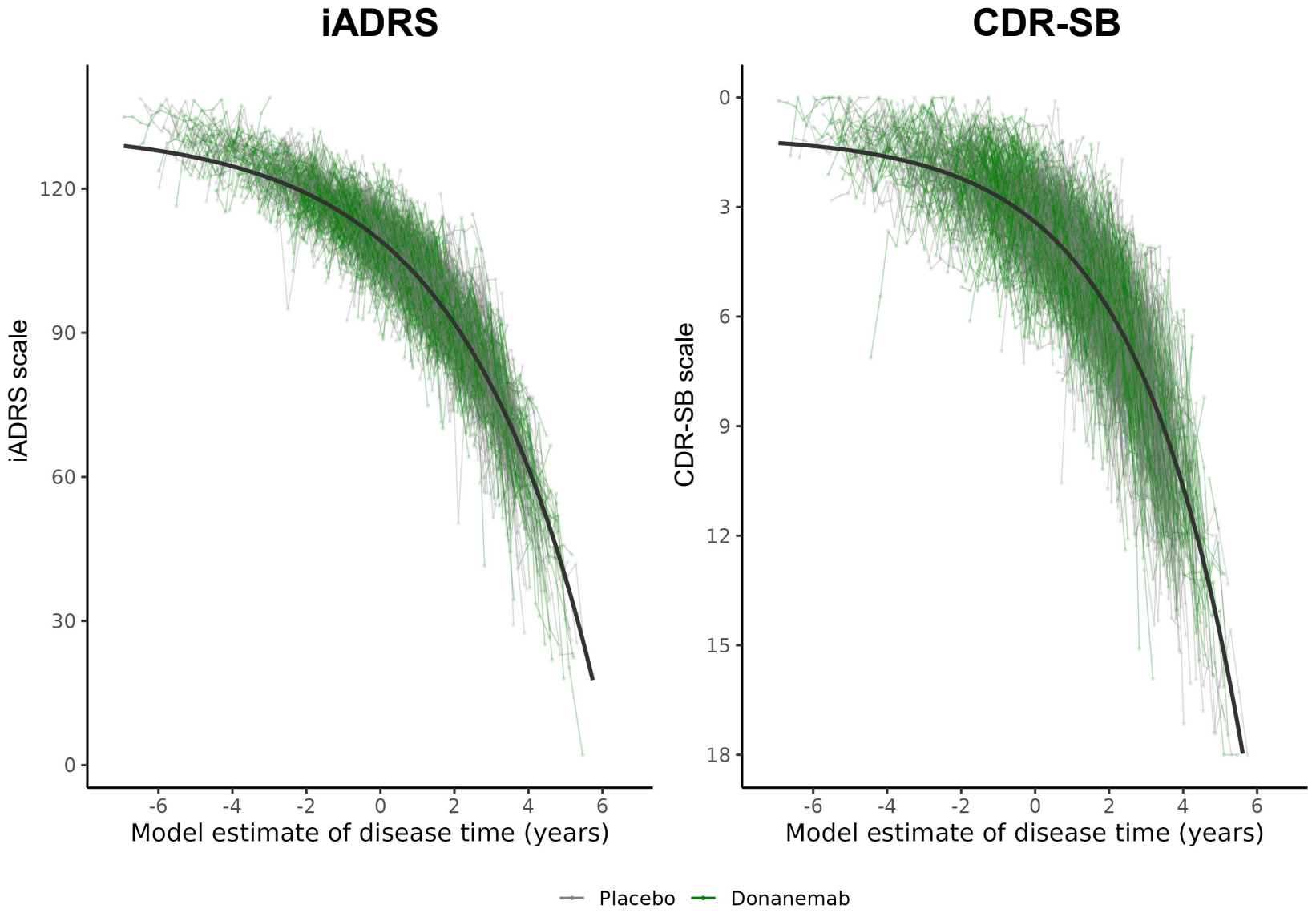
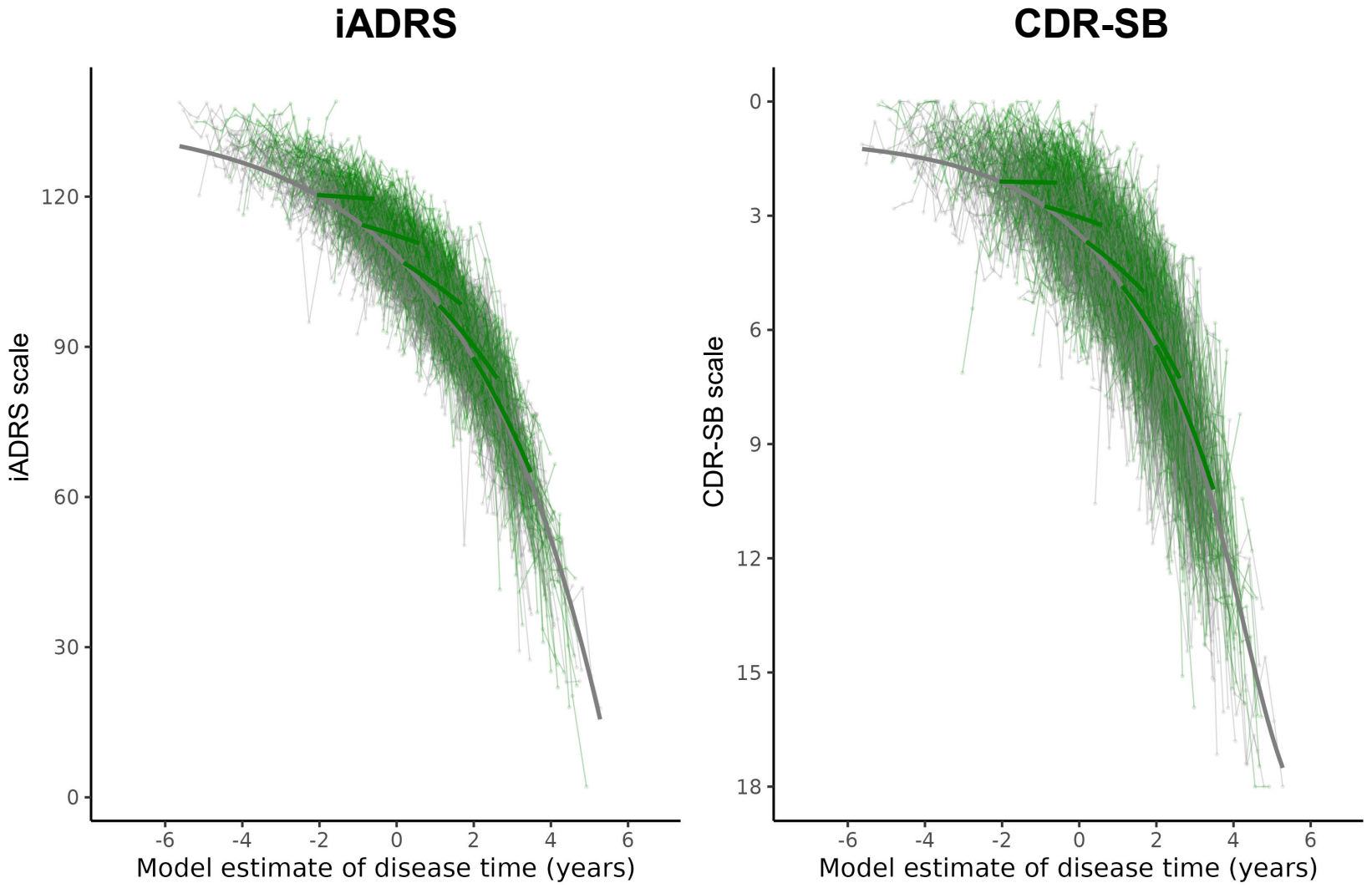


[1] Kühnel et al, Statistics in Medicine 2021

Finding structure in trajectories of decline – modeling treatment

- **Natural history trajectories were modeled based on placebo treated participants as just described**
  - Trajectories of donanemab treated participants modeled as proportional to the natural history trajectory
  - Treatment effects modeled as time savings[1]
  - Time savings allowed to vary non-monotonically by disease stage at treatment initiation (3 parameters per outcome) allowed



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[1] Raket., Statistics in Medicine 2022

Finding structure in trajectories of decline – modeling treatment

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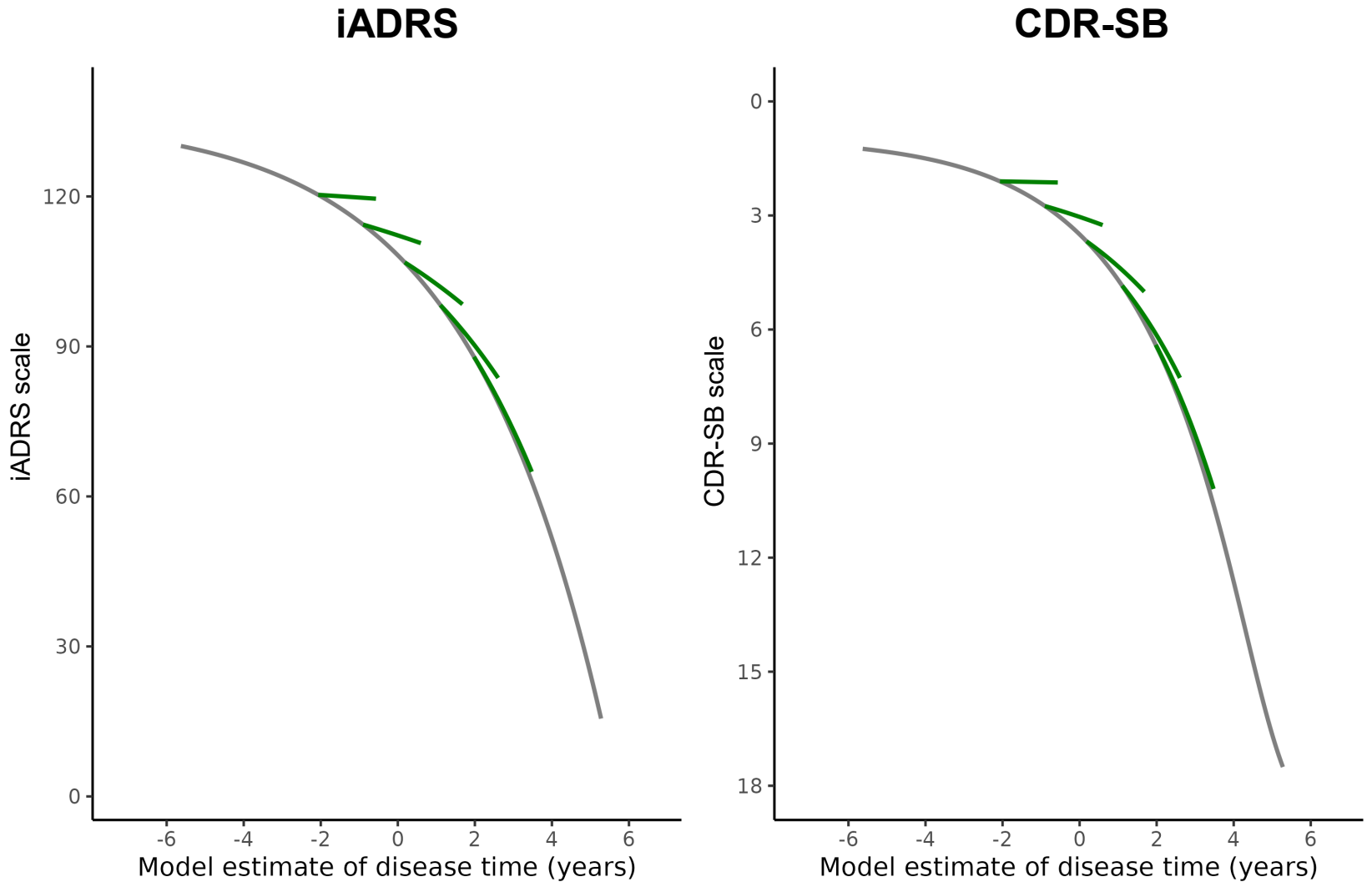

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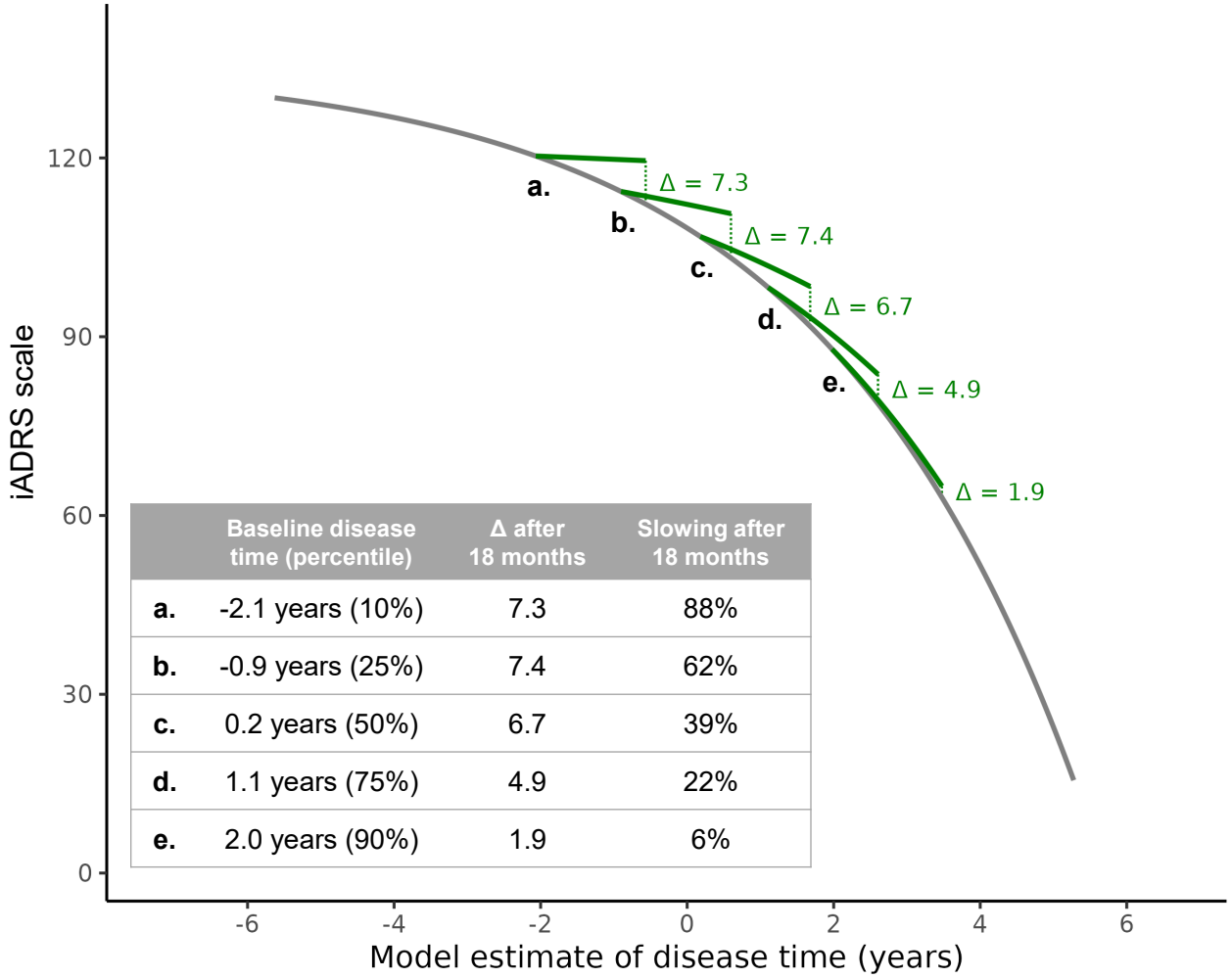
[1] Raket., Statistics in Medicine 2022

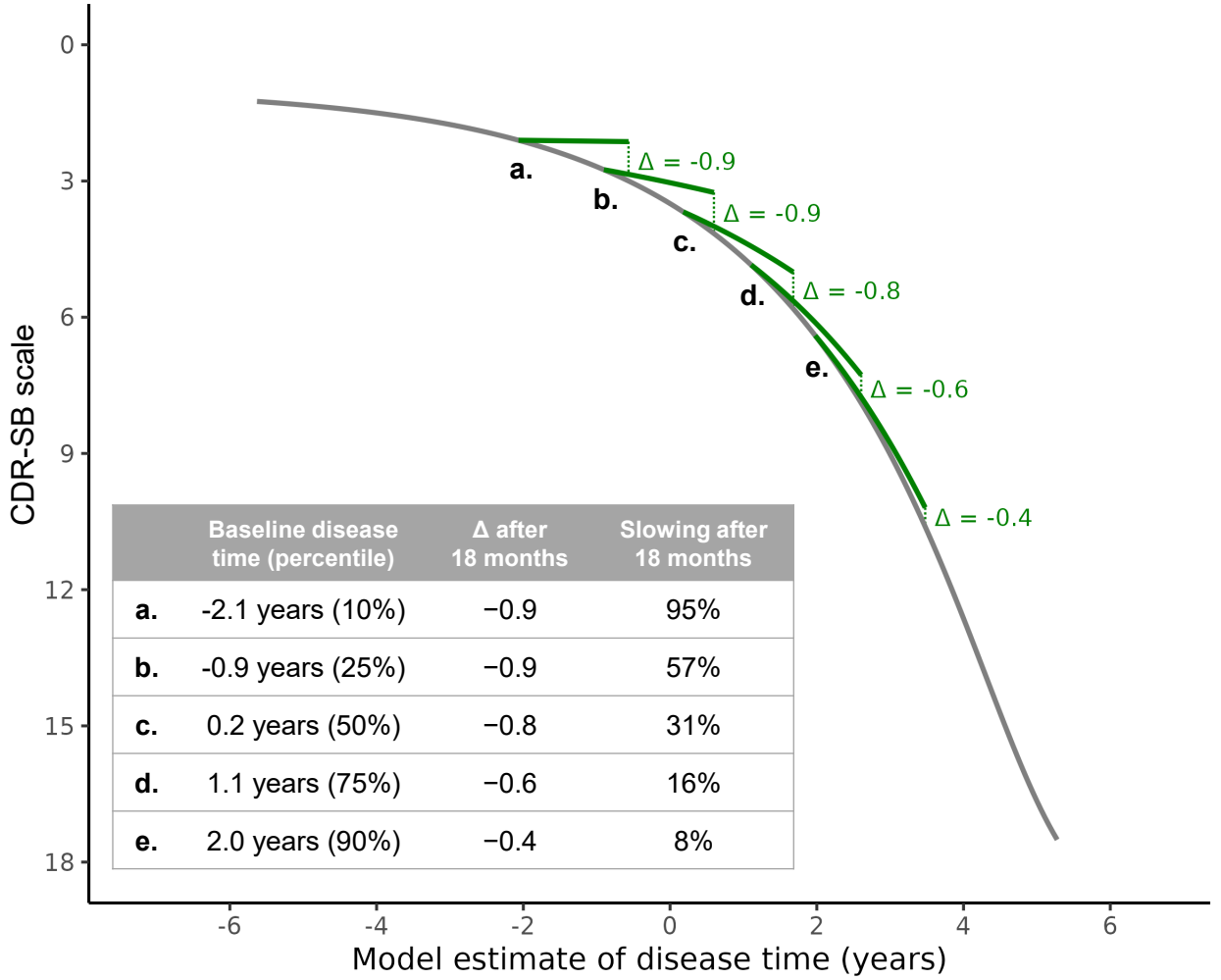
Estimating stage-dependent treatment effects

iADRS



	Baseline disease time (percentile)	Δ after 18 months	Slowing after 18 months
a.	-2.1 years (10%)	7.3	88%
b.	-0.9 years (25%)	7.4	62%
c.	0.2 years (50%)	6.7	39%
d.	1.1 years (75%)	4.9	22%
e.	2.0 years (90%)	1.9	6%

CDR-SB



	Baseline disease time (percentile)	Δ after 18 months	Slowing after 18 months
a.	-2.1 years (10%)	−0.9	95%
b.	-0.9 years (25%)	−0.9	57%
c.	0.2 years (50%)	−0.8	31%
d.	1.1 years (75%)	−0.6	16%
e.	2.0 years (90%)	−0.4	8%

Placebo — Donanemab

Summary – TRAILBLAZER-ALZ 2

- Taken together, baseline characteristics that are indicative of early disease stage (lower tau, age and plasma P-tau217) are associated with greater donanemab-mediated slowing of disease progression.
- Treatment benefits are observed across the spectrum of baseline characteristics.

Clinical Relevance of Donanemab Treatment

Alireza Atri[1,2], Alette Wessels[3], Alexandra Atkins[3], Julie Chandler[3], Ming Lu[3], Wenyu Ye[3], Ellen B. Dennehy[3], Dawn Brooks[3], John Sims[3]

[1]Banner Sun Health Research Institute and Banner Alzheimer's Institute, Sun City and Phoenix, AZ, USA
[2]Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA
[3]Eli Lilly and Company, Indianapolis, IN, USA

Clinical Trials on Alzheimer's Disease (CTAD) – 16th Annual Conference
Boston, Massachusetts, USA, and Online
October 24 - 27, 2023

Sponsored by Eli Lilly and Company

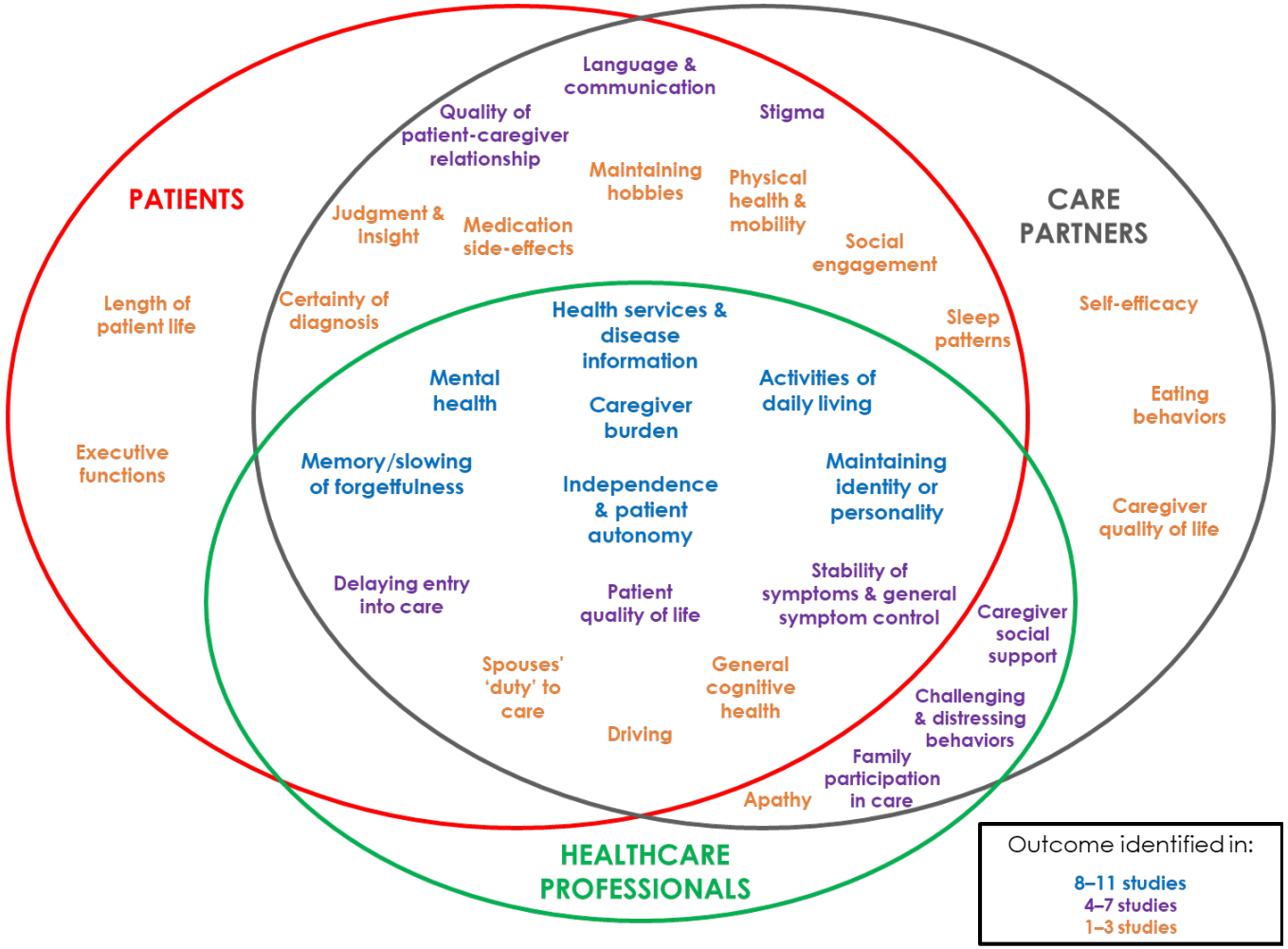
Presenter's Disclosure

- Alireza Atri, MD, PhD has received consulting-related honoraria or travel in the past 10 years from AbbVie, Acadia, Allergan, Axovant, AZ Therapies, Biogen, Eisai, Grifols, JOMDD, Lundbeck, Merck, Roche/Genentech, Novo Nordisk, Prothena, Qynapse, Sunovion, Suven, and Synexus.
- Dr. Atri has received book royalties from Oxford University Press for a medical book on dementia.
- Dr. Atri was a site PI for the A4 study (solanezumab – Lilly).
- Dr. Atri is not receiving honoraria or travel support for this work and presentation.

What outcomes are valued by patients, care partners and HCPs?

- With the advent of disease-modifying therapy, slowing of disease progression is possible, but clinical trial endpoints may not be easily interpretable by clinicians, patients, and their care partners
  - Surveys of patients, care partners, and clinicians endorse the value of slowing disease progression to remain at earlier stages of disease longer, maintaining their level of independence and ability to participate in activities that matter most to them[1-5]

Outcomes Valued According to Stakeholder Group



Data from Tochel C, et al; ROADMAP consortium. *Alzheimers Dement (Amst)*. 2019;11:231-247.

[1]Tochel et al Alzheimers Dement 2019; 7:11:231-247
[2]DiBenedetti et al Alzheimers Res & Ther 2020;12:90
[3]Hauber et al Neurol Ther 2023;12:505–527
[4]Jessen et al J Prev Alz Dis 2022;9:550-555
[5]Watson et al Health Expectations 2019 22:504-517
Abbreviation: HCP=healthcare professionals

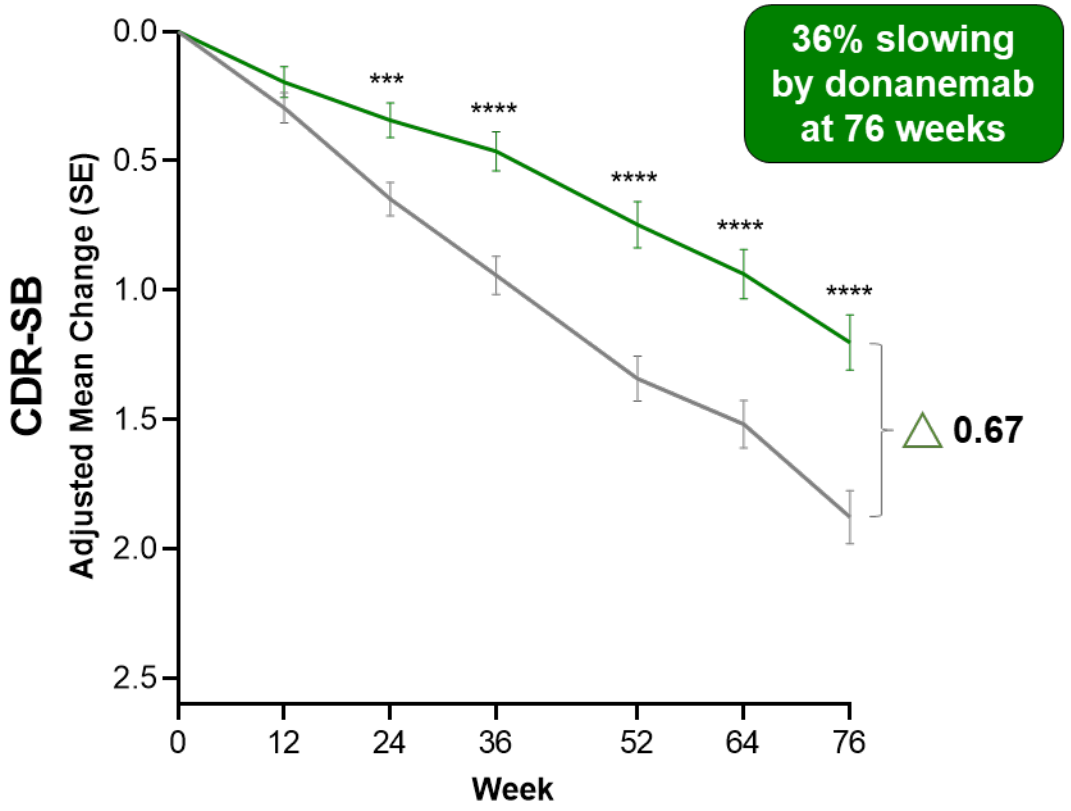
What is known about clinical relevance of donanemab treatment?

- In TRAILBLAZER-ALZ 2, the clinical relevance of donanemab treatment was demonstrated by
  - *slowing of clinical decline (percent reduction / time saved)*
  - *stability of clinical symptoms*
  - *lower risk of advancement to the next clinical stage*
  - *lower risk of meaningful within-patient change*

- This presentation will address further insights derived from exploratory post-hoc analyses into the clinical meaningfulness of donanemab treatment

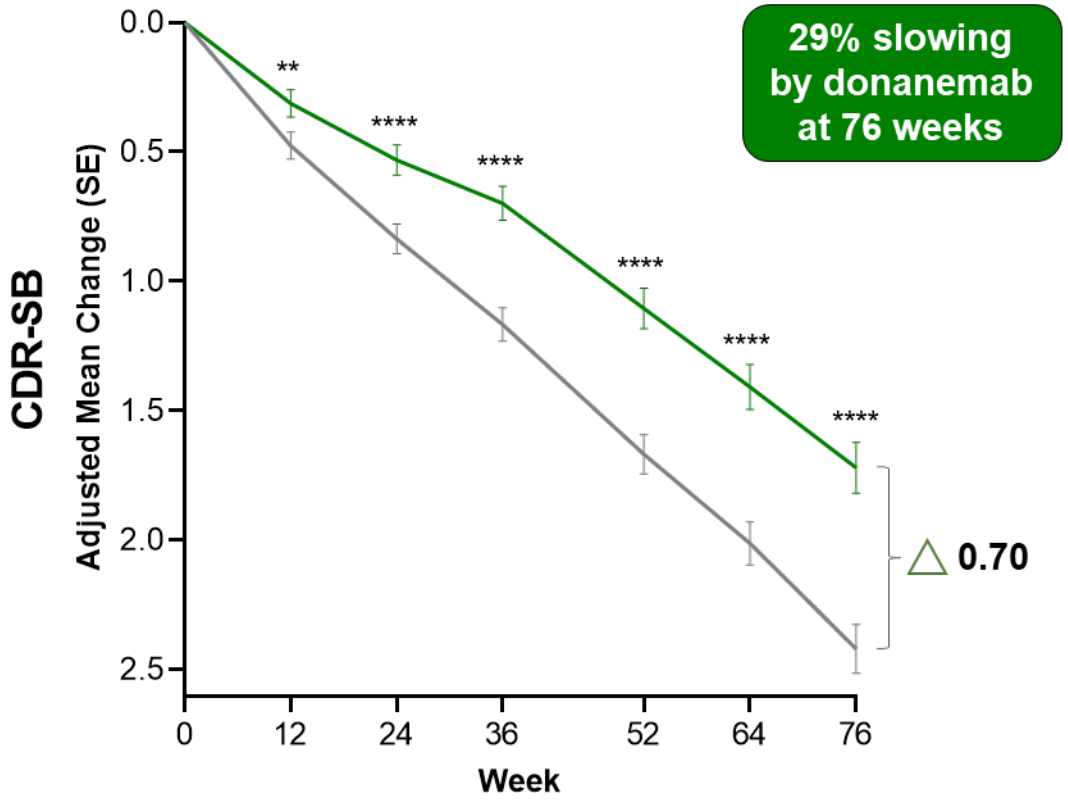
Effect of donanemab on measures of global disease severity

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 population



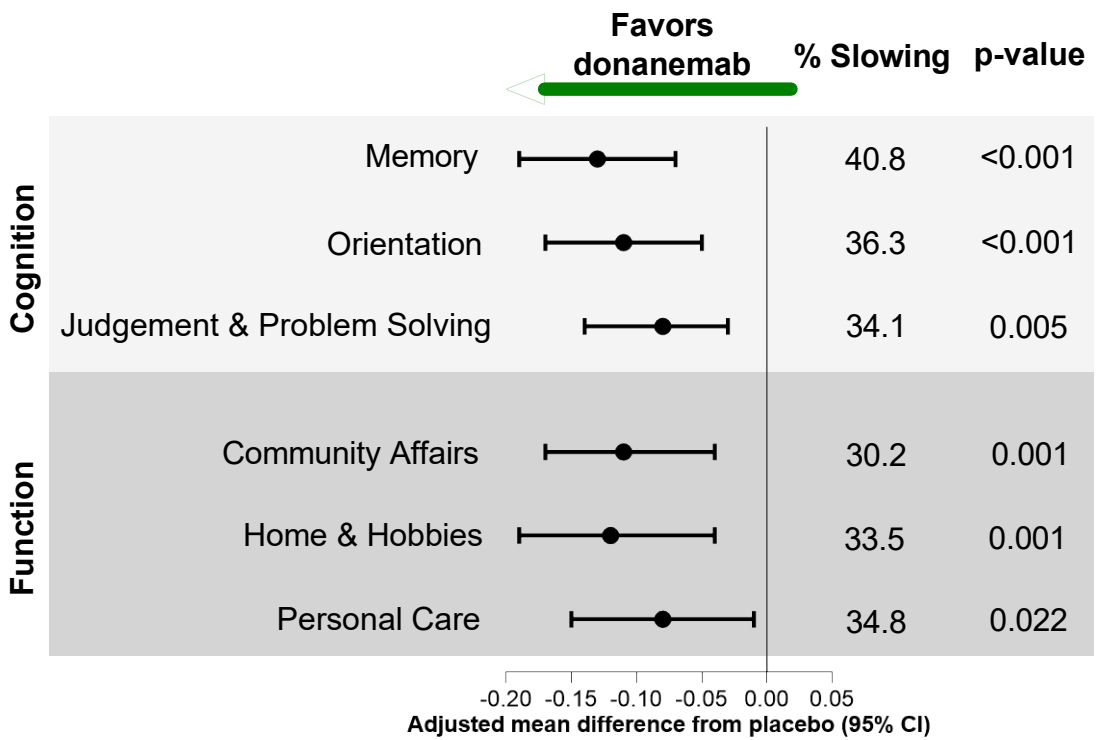
Placebo	838	825	784	752	713	678	672
Donanemab	794	774	731	682	650	603	598

Sims et al JAMA 2023;330(6):512-527
AAIC 2023 TRAILBLAZER-ALZ 2 Symposium
Abbreviations: CDR-SB=Clinical Dementia Rating–Sum of Boxes; SE=standard error
**P<0.01; ***P<0.001; ****P<0.0001

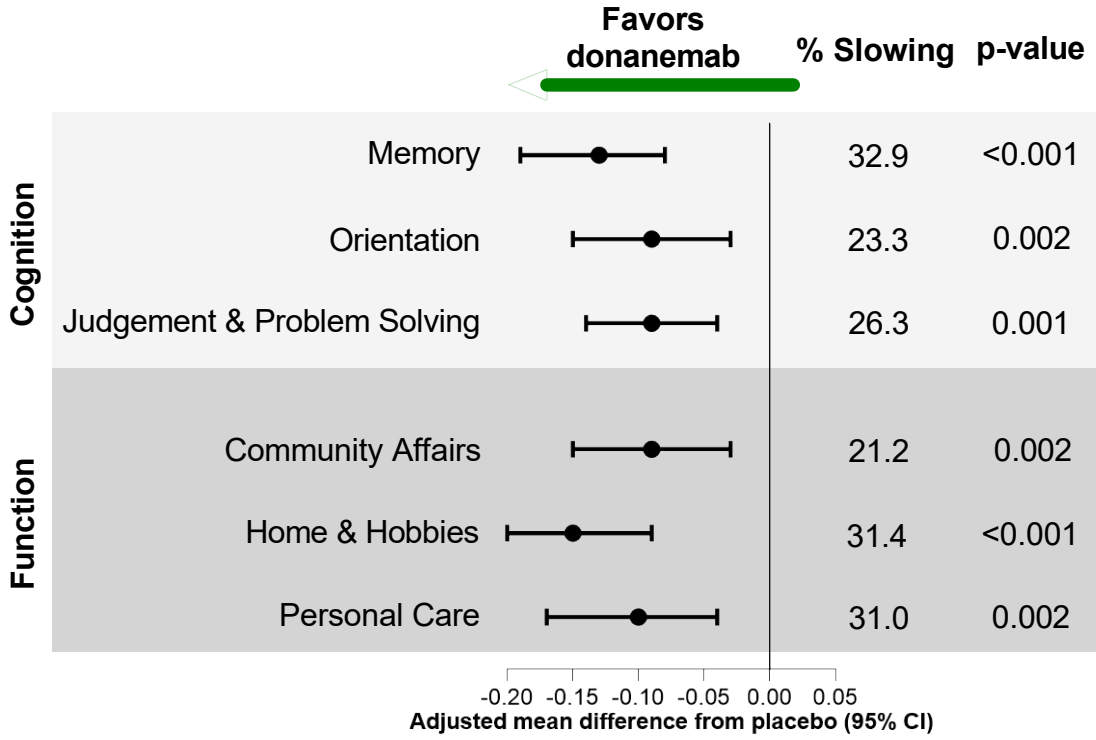
Clinically relevant treatment effect seen across all CDR-SB domains

CDR-SB domains at 76 weeks

Low-medium tau population



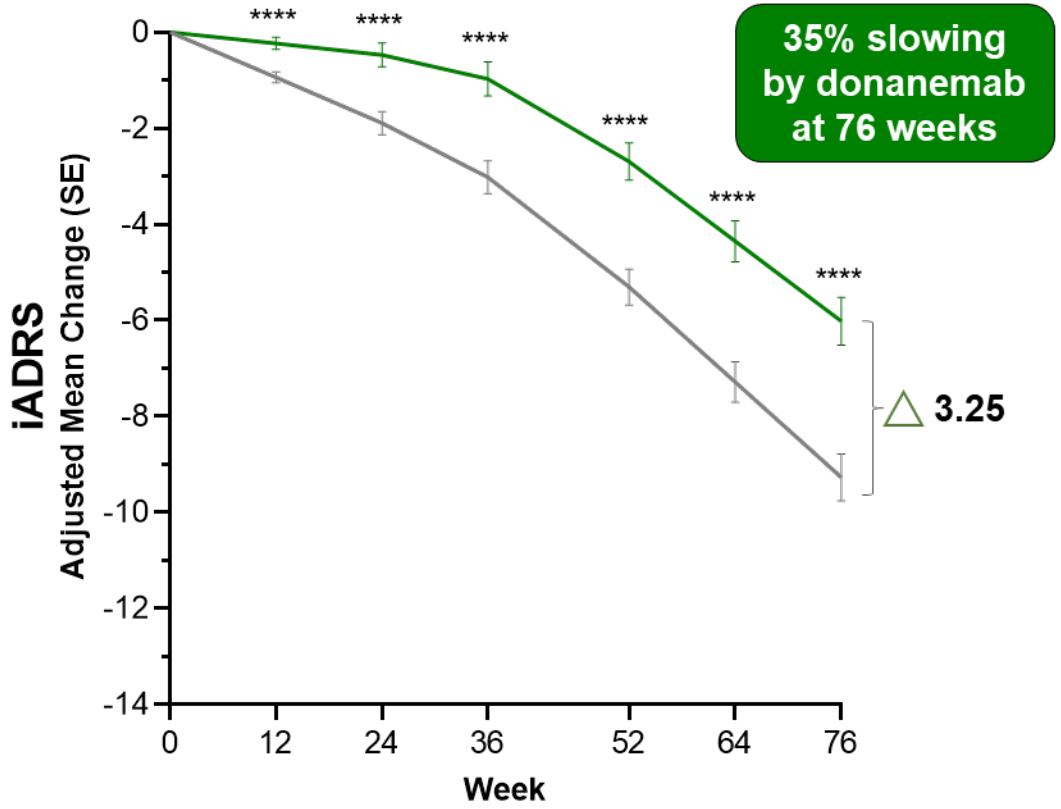
Combined population



Number of participants at 76 weeks: Low-medium tau placebo 459, donanemab 424; Combined population placebo 672, donanemab 598.
Abbreviations: CDR-SB=Clinical Dementia Rating–Sum of Boxes; CI=confidence interval

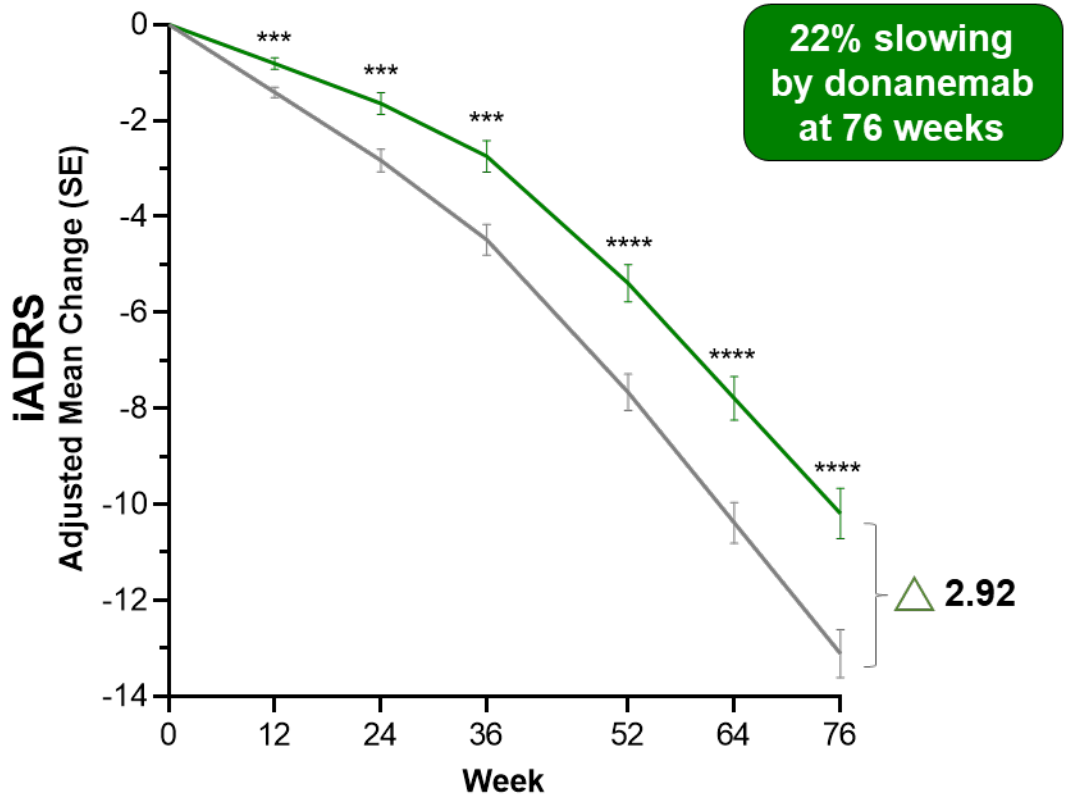
Effect of donanemab on measures of global disease severity

iADRS: Low-medium tau population



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

iADRS: Combined population



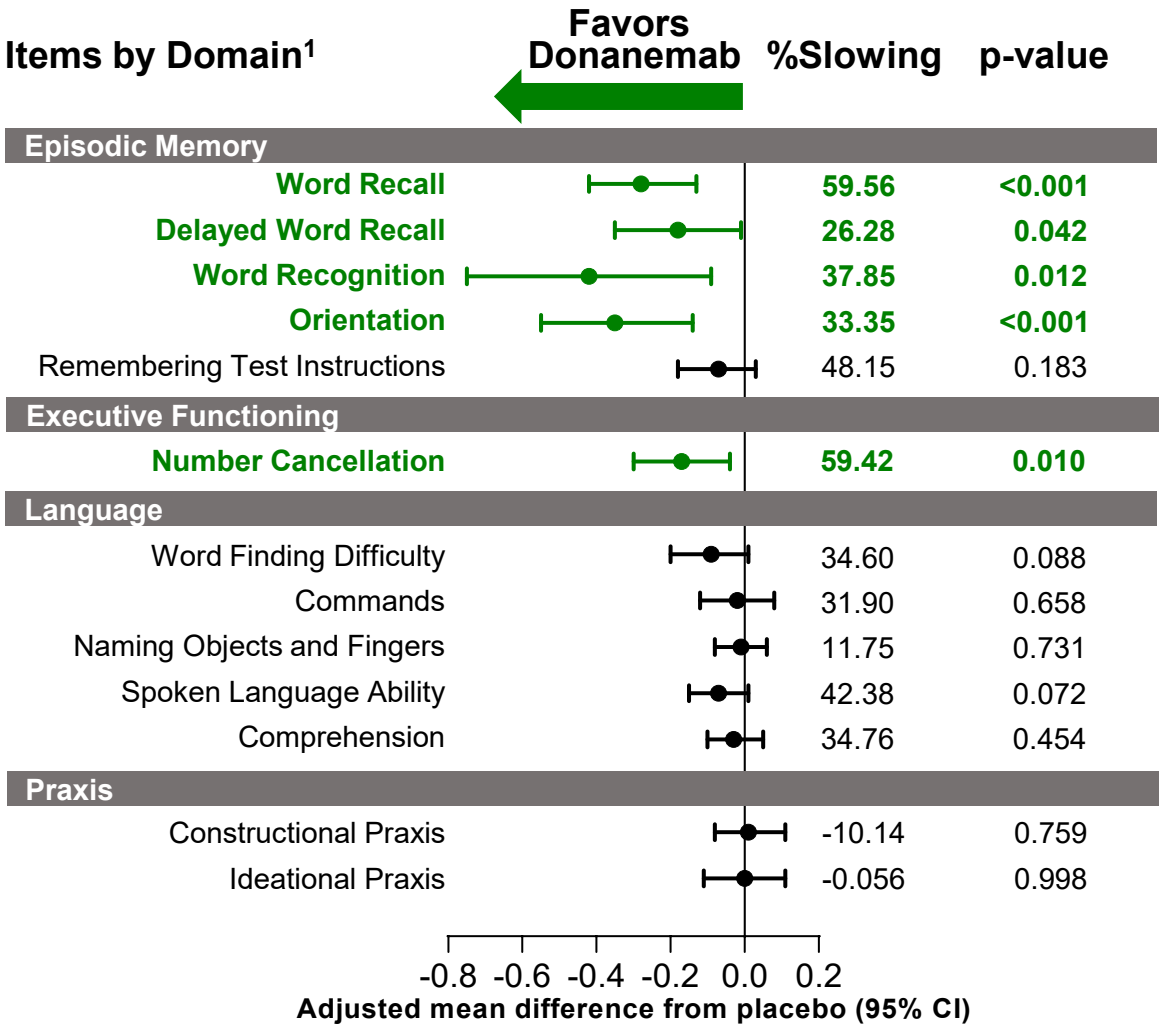
Placebo	824	805	767	738	693	651	653
Donanemab	775	752	712	665	636	579	583

Sims et al JAMA 2023;330(6):512-527
AAIC 2023 TRAILBLAZER-ALZ 2 Symposium
Abbreviations: iADRS=integrated Alzheimer's Disease Rating Scale; SE=standard error
***P<0.001; ****P<0.0001

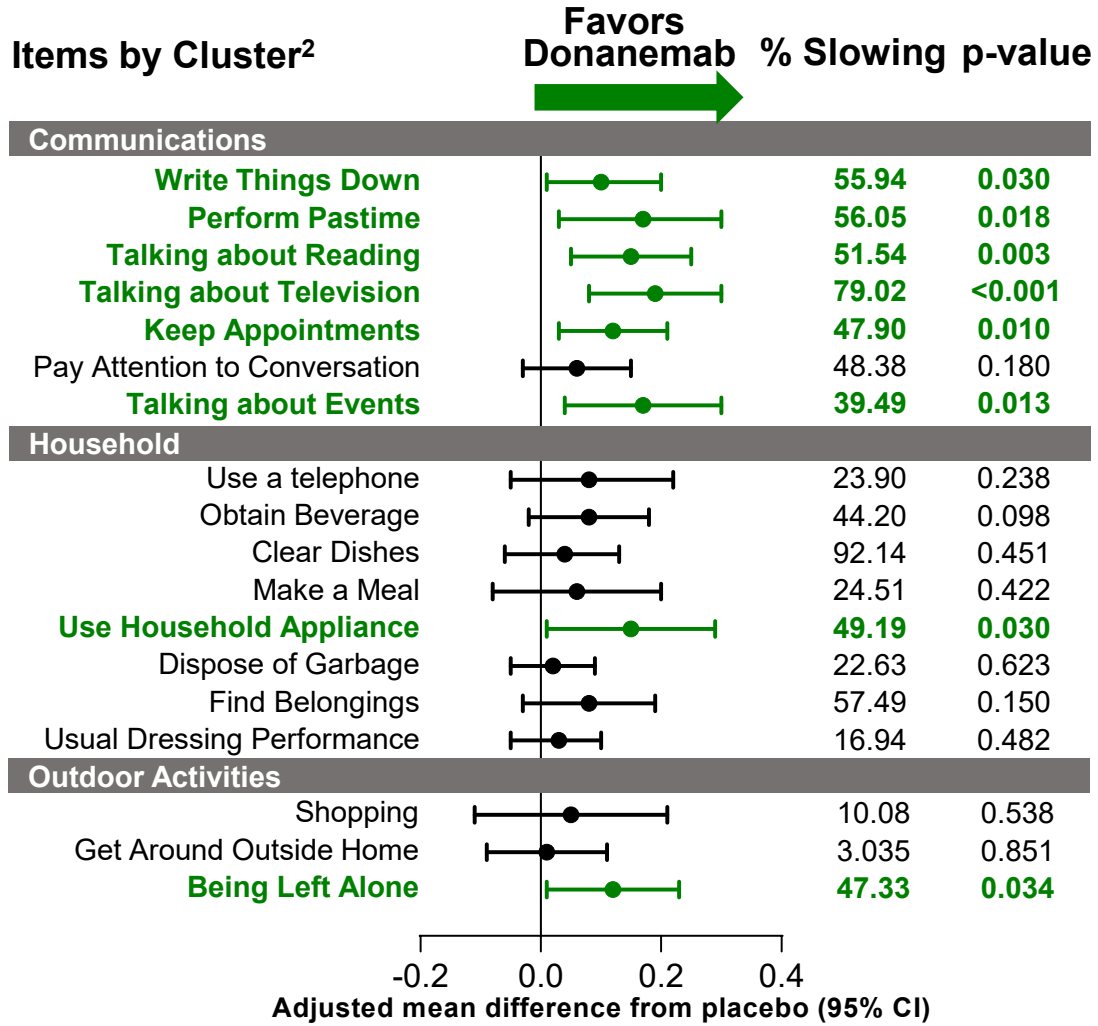
Cognition (ADAS-Cog$_{13}$) and Daily function (ADCS-iADL) item score

Low-medium tau population

Cognition: ADAS-Cog$_{13}$ Individual Item Score



Daily function: ADCS-iADL Individual Item Score



[1]Rosen et al Am J Psychiatry 1984; 141(11):1356-64 and Mohs et al Alzheimer Dis Assoc Disord 1997; 11 Suppl 2: S13-21
[2]Kahle-Wrobleski et al Curr Alzheimer's Res 2014; 11:357-366

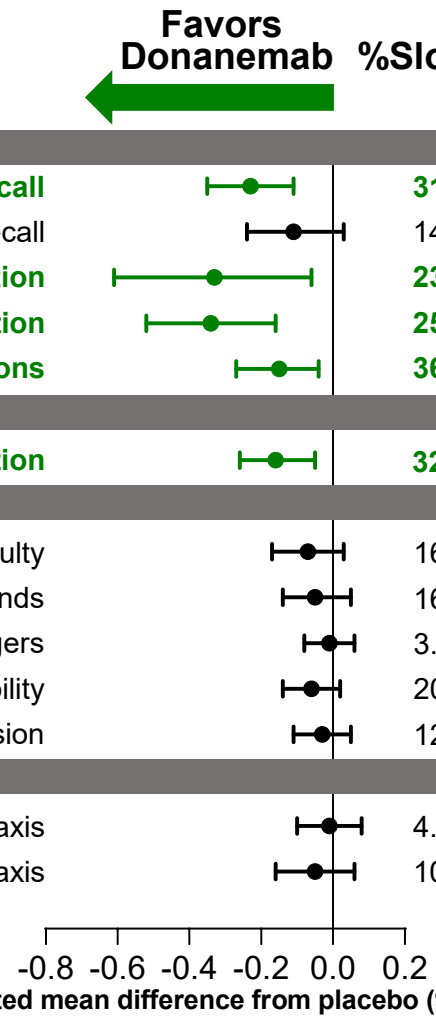
Abbreviations: ADAS-Cog$_{13}$=Alzheimer's Disease Assessment Scale - Cognitive subscale; ADCS-iADL=Alzheimer's Disease Cooperative Study-instrumental Activities of Daily Living Inventory; CI=confidence interval;

Cognition (ADAS-Cog$_{13}$) and Daily function (ADCS-iADL) item score

Combined population

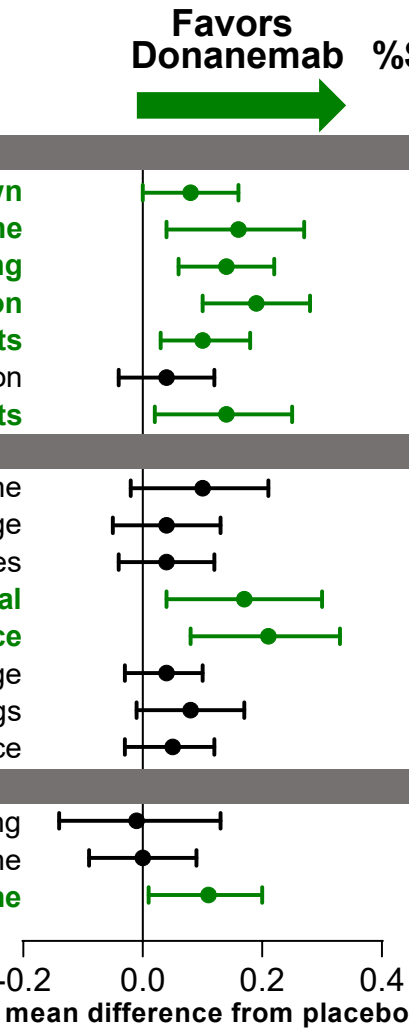
Cognition: ADAS-Cog$_{13}$ Individual Item Score

Items by Domain[1]	%Slowing	p-value
Episodic Memory		
Word Recall	**31.94**	**<0.001**
Delayed Word Recall	14.76	0.121
Word Recognition	**23.14**	**0.017**
Orientation	**25.24**	**<0.001**
Remembering Test Instructions	**36.33**	**0.010**
Executive Functioning		
Number Cancellation	**32.54**	**0.004**
Language		
Word Finding Difficulty	16.04	0.152
Commands	16.69	0.336
Naming Objects and Fingers	3.451	0.833
Spoken Language Ability	20.36	0.170
Comprehension	12.26	0.500
Praxis		
Constructional Praxis	4.150	0.769
Ideational Praxis	10.44	0.375



Daily function: ADCS-iADL Individual Item Score

Items by Cluster[2]	%Slowing	p-value
Communications		
Write Things Down	**28.59**	**0.043**
Perform Pastime	**34.75**	**0.010**
Talking about Reading	**40.14**	**<0.001**
Talking about Television	**64.32**	**<0.001**
Keep Appointments	**32.53**	**0.008**
Pay Attention to Conversation	18.15	0.379
Talking about Events	**29.35**	**0.020**
Household		
Use a telephone	19.47	0.098
Obtain Beverage	13.65	0.376
Clear Dishes	33.68	0.318
Make a Meal	**32.25**	**0.010**
Use Household Appliance	**39.90**	**0.001**
Dispose of Garbage	23.48	0.278
Find Belongings	36.31	0.065
Usual Dressing Performance	17.98	0.207
Outdoor Activities		
Shopping	-1.123	0.921
Get Around Outside Home	-0.491	0.964
Being Left Alone	**33.91**	**0.031**



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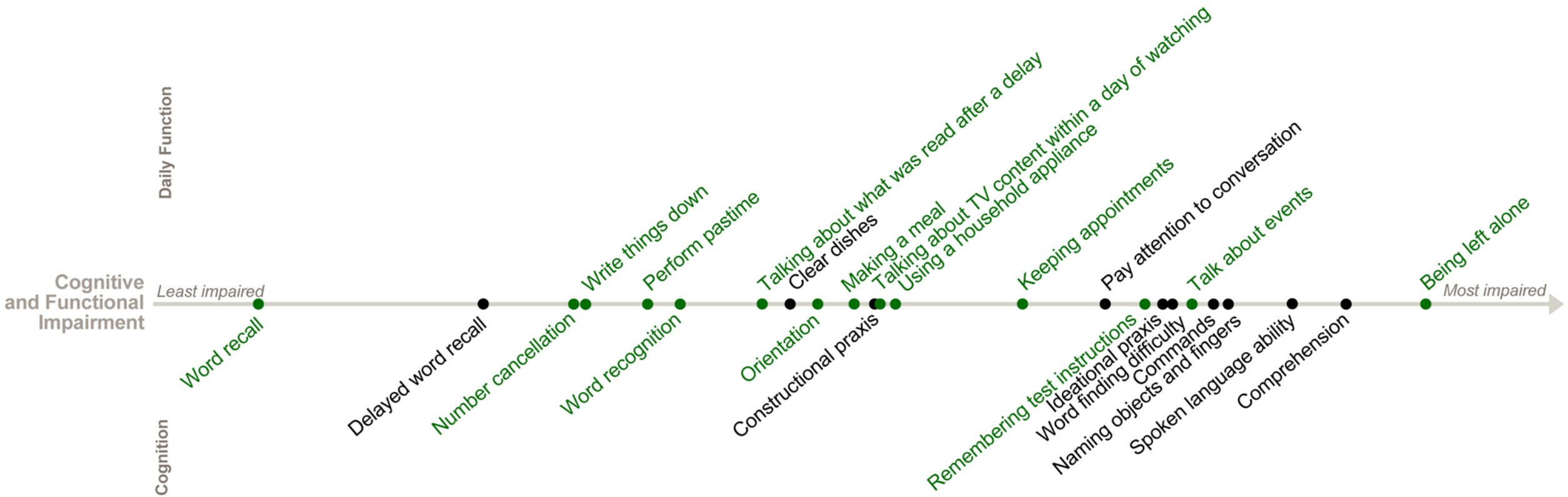
Abbreviations: ADAS-Cog$_{13}$=Alzheimer's Disease Assessment Scale - Cognitive subscale; ADCS-iADL=Alzheimer's Disease Cooperative Study-instrumental Activities of Daily Living Inventory; CI=confidence interval;

Slowing of progression on iADRS items with donanemab treatment

Combined population

Hierarchy of expected changes in iADRS items in early symptomatic AD



Items in green have significant % slowing in the combined population with donanemab treatment compared to placebo

*not a complete list of iADRS items. A probabilistic Rasch model was used to examine the extent to which the observed data (actual responses to scale items) 'fit' predictions of those responses from the Rasch model[1] RMT was performed in RUMM2030 (Rummlab Pty Ltd). All 31 iADRS items were included in a single RMT model; item response thresholds for *cognitive* (items going down) and *daily function* (items going up) are shown.

[1]Andrich et al Sage Publications 1988:07-068

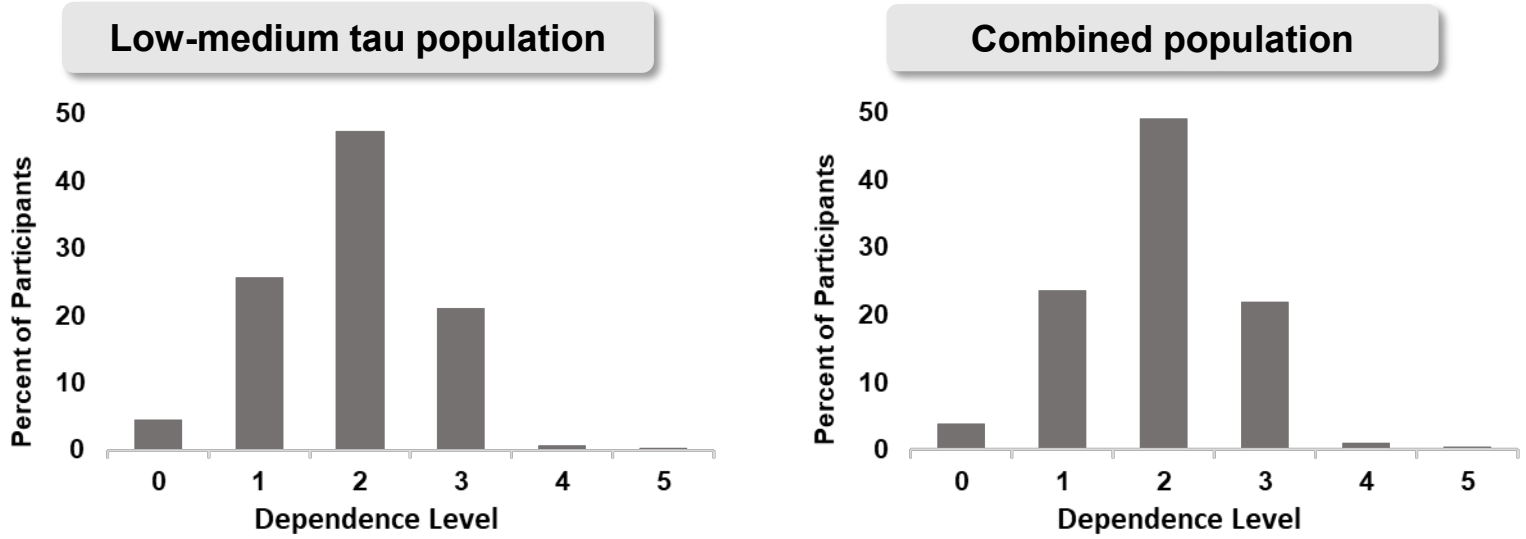
Abbreviations: AD=Alzheimer's disease; iADRS=Integrated Alzheimer's Disease Rating Scale

Categorizing participants by levels of dependence

Mapping of ADCS-ADL Items to Levels of Dependence and Projected Care[1]

0 FULLY INDEPENDENT	1 MOSTLY INDEPENDENT	2 MILDLY DEPENDENT	3 MODERATELY DEPENDENT	4 MOSTLY DEPENDENT	5 FULLY DEPENDENT
No care needs.	Informal visits/check-ins for those living alone	Limited formal or informal in-home support	Moderate in-home support or assisted living	Extensive in-home care or assisted living + supplemental 1:1 care / nursing	24-hour care/supervision required (nursing facility or private residence)
Autonomous in all instrumental and basic ADLs	Reminders/ support for *isolated* iADLs only	Reminders/ support for *multiple* iADLs	Physical help needed for multiple iADLs; Reminders or supervision for bADLs	Physical help needed for multiple bADLs	Reliant on others for basic needs (eating, walking or toileting)

TRAILBLAZER-ALZ 2 Distribution of Dependence Level at Baseline

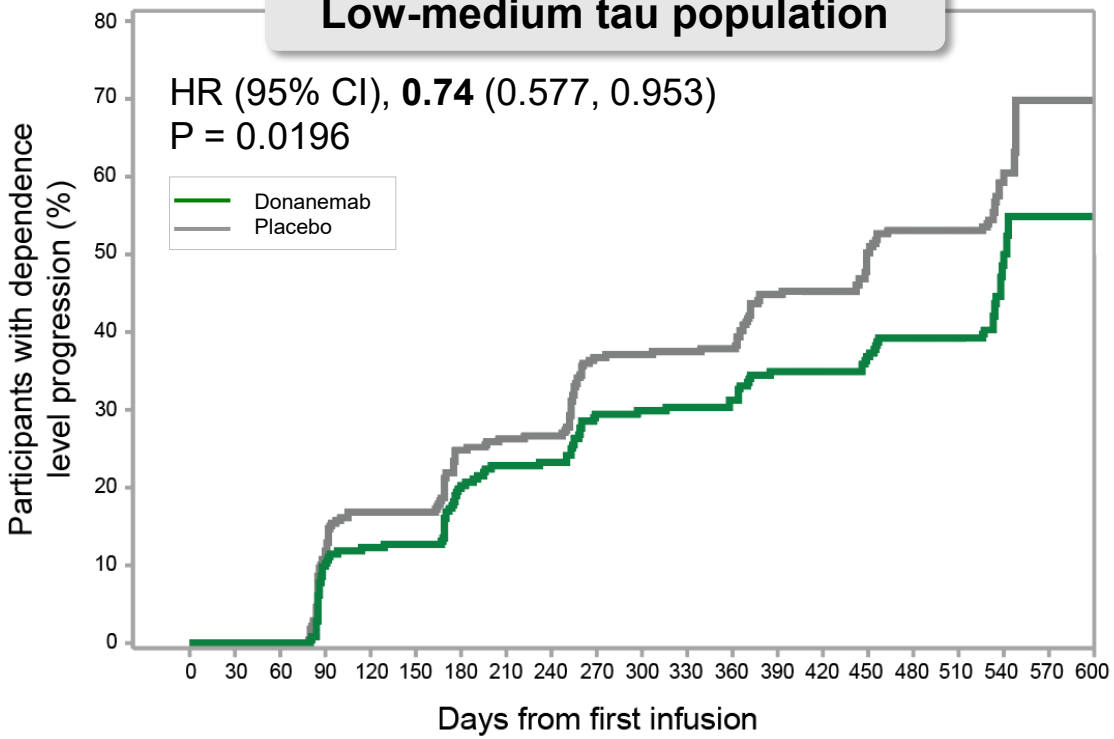


[1]Dependence level classification algorithm based on ongoing collaboration with F. Hoffmann-La Roche Ltd., adapted from Kahle-Wrobleski et al J Prev Alzheimers Dis 2015; 2(2):115-120 and McDougall et al Value in Health 2022;25(12, Supplement):S48-S9.
Abbreviations: ADCS-ADL=Alzheimer's Disease Cooperative Study-Activities of Daily Living Inventory; bADL= basic Activities of Daily Living; iADL=instrumental Activities of Daily Living

Risk reduction for progression to next dependence level for participants with baseline dependence level 2

Dependence Level 2 MILDLY DEPENDENT
Limited formal or informal in-home support
Frequent reminders/ support for multiple iADLs

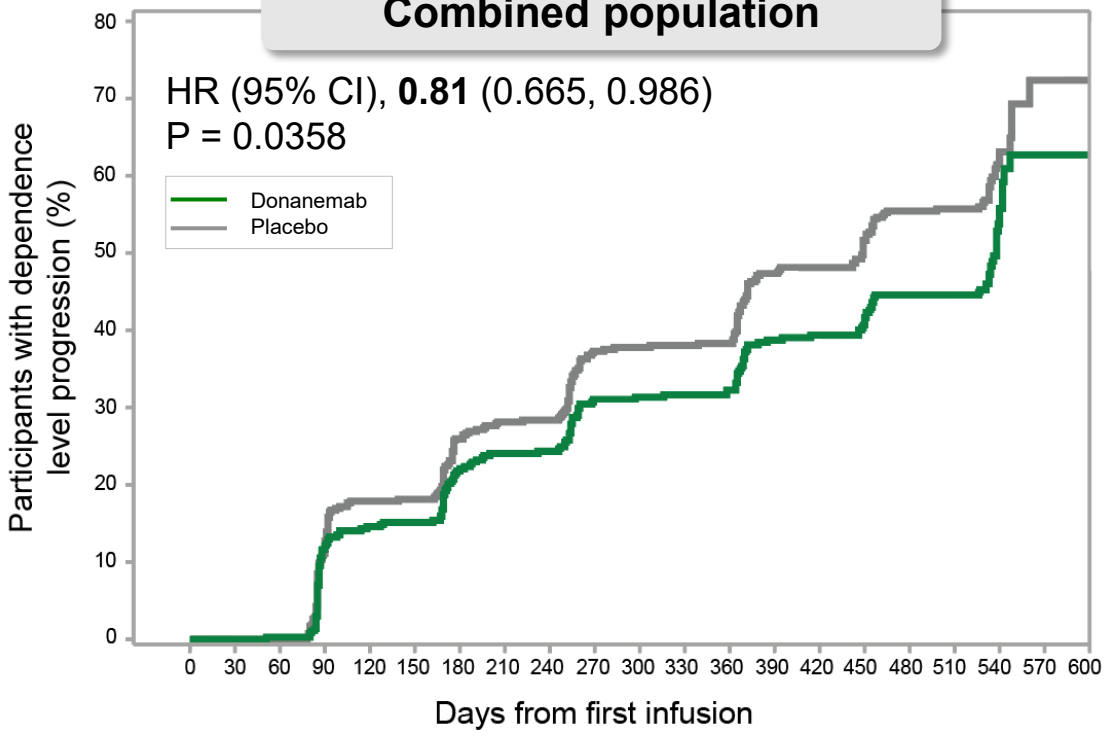
Low-medium tau population



Placebo Participant N=280, Event n=156 (55.7%)
Donanemab Participant N=246, Event n=105 (42.7%)

26% lower risk of progression over 76 weeks

Combined population



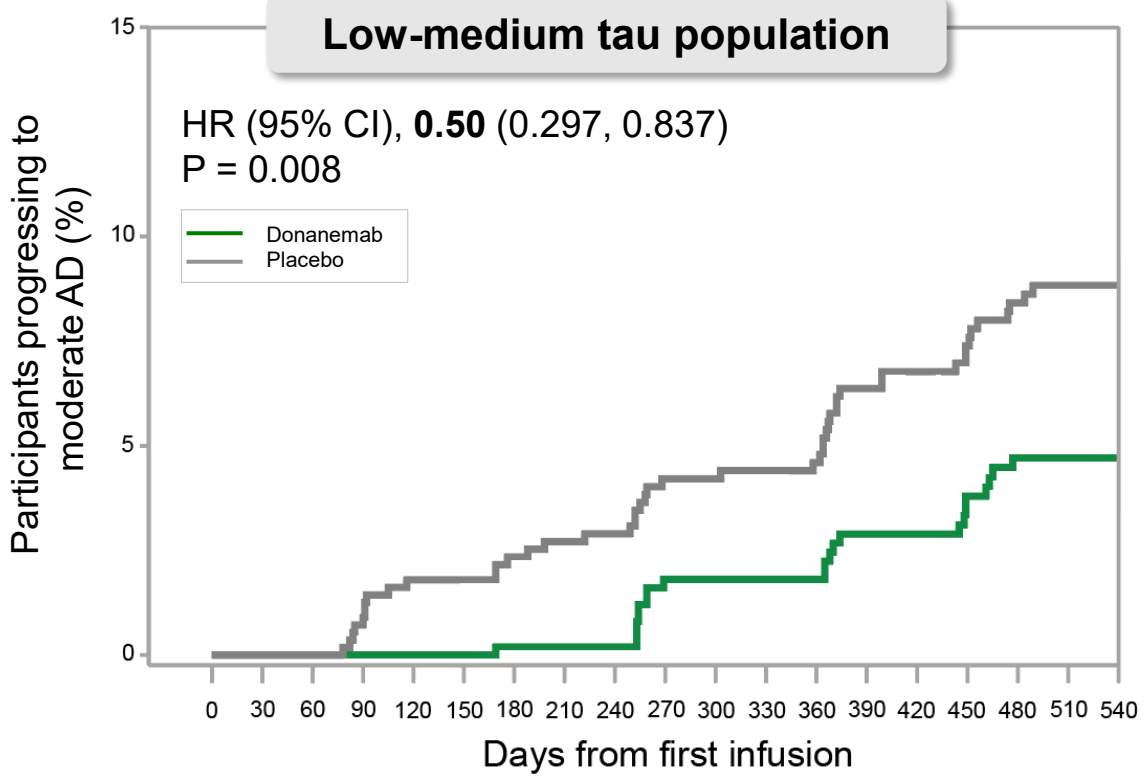
Placebo Participant N=426, Event n=247 (58.0%)
Donanemab Participant N=372, Event n=177 (47.6%)

19% lower risk of progression over 76 weeks

Abbreviations: CI=confidence interval; HR=hazard ratio; iADL=instrumental Activities of Daily Living; n=event number; N=number of participants

Risk reduction for progression to moderate dementia due to AD (CDR-G ≥ 2)

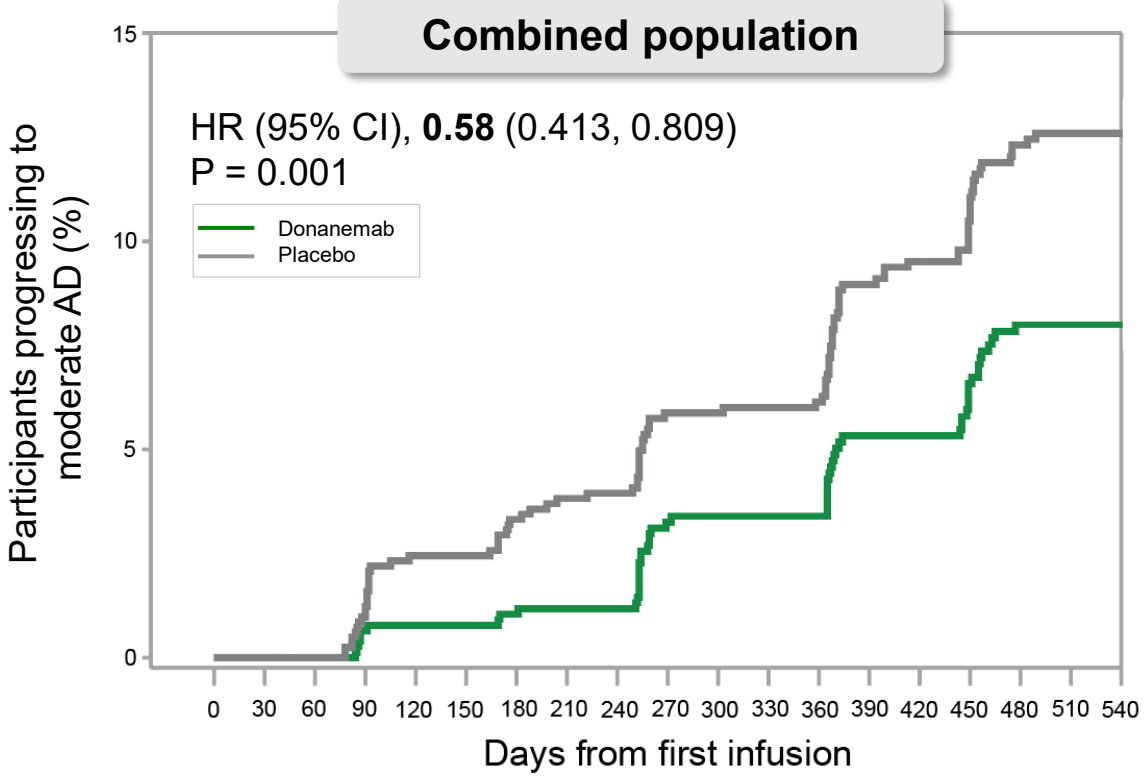
Low-medium tau population



Placebo Participant N=559, Event n=46 (8.2%)
Donanemab Participant N=538, Event n=22 (4.1%)

50% lower risk of progression over 76 weeks

Combined population



Placebo Participant N=821, Event n=96 (11.7%)
Donanemab Participant N=784, Event n=55 (7.0%)

42% lower risk of progression over 76 weeks

Abbreviations: AD=Alzheimer's disease; CDR-G=Clinical Dementia Rating-global; CI=confidence interval; HR=hazard ratio; n=event number; N=number of participants

Conclusions

In addition to previously disclosed demonstrations of clinical relevance, these post-hoc analyses from TRAILBLAZER-ALZ 2 further illustrate the benefit of donanemab treatment in early symptomatic AD.

- Benefits of donanemab treatment seen across all 6 domains of the CDR-SB, and across individual cognitive and functional iADRS items.
- Donanemab treatment results in significantly lower risk of progression to moderate dementia.
- Donanemab treatment significantly lowers risk of progression to higher levels of dependency.
- Benefits demonstrated across multiple analytic approaches, outcomes, and populations support that slowing of clinical decline with donanemab treatment translates into meaningful benefits for patients.

Abbreviations: AD=Alzheimer's disease; CDR-SB=Clinical Dementia Rating–Sum of Boxes; iADRS=integrated Alzheimer's Disease Rating Scale

Symposium Conclusions

- The post-hoc exploratory analyses continue to reflect that donanemab treatment slows cognitive and functional decline across multiple populations of participants with early symptomatic Alzheimer's Disease, with safety findings consistent with the class of amyloid-targeting therapies.
- The hypothesis-generating analyses further refine our understanding of the translational value of amyloid-targeting therapies by demonstrating that:
  - There are key baseline variables associated with ARIA-E frequency in donanemab-treated participants.
  - Baseline characteristics indicative of early disease stage are associated with greater donanemab-mediated slowing of disease progression.
  - Clinical outcome measures are associated with benefits that matter to patients and loved ones.

Panel Discussion and Question & Answer Session

Moderated by Takeshi Iwatsubo

Graduate School of Medicine, The University of Tokyo, Tokyo

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Boston, Massachusetts, USA, and Online
October 24 - 27, 2023

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