Efficacy of Donanemab by *APOE ε4* Carrier Status in TRAILBLAZER-ALZ 2, a Phase 3 Randomized Clinical Trial in Early Symptomatic Alzheimer's Disease

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Presenter's Disclosure

- Cynthia D. Evans is an employee and minor shareholder 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.

Acknowledgments

- Eli Lilly and Company would like to thank the clinical trial participants and their study partners, without whom this work would not be possible.
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- This study was sponsored by Eli Lilly and Company.

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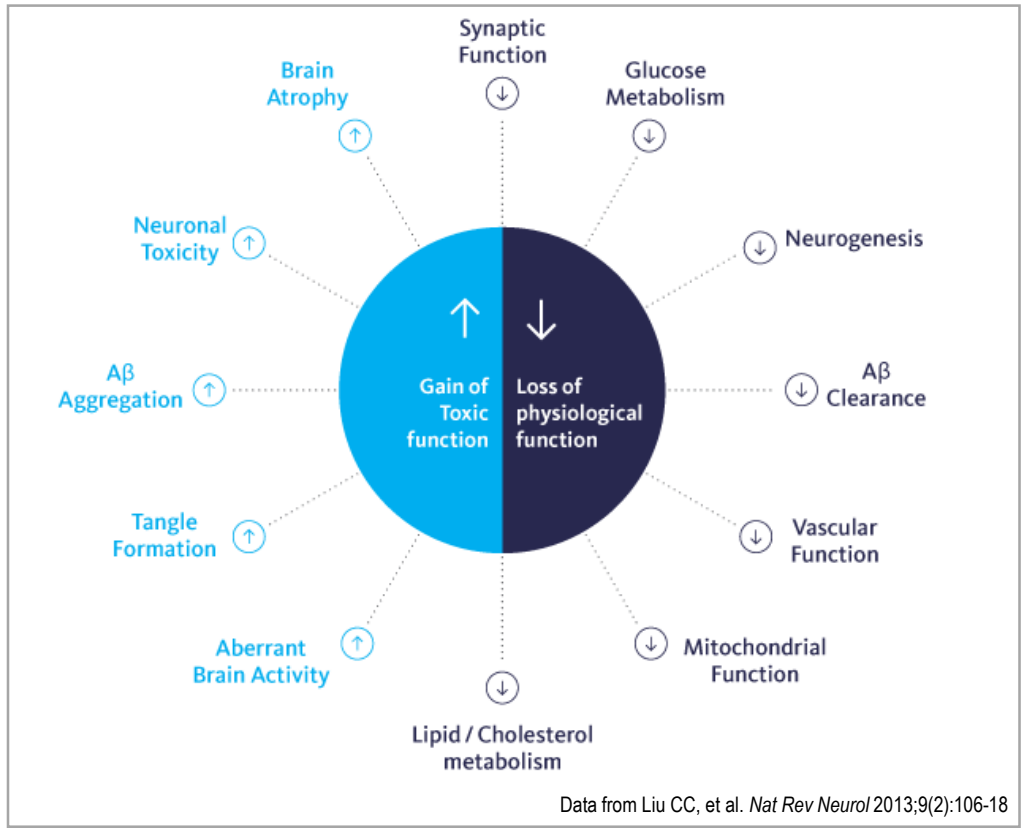
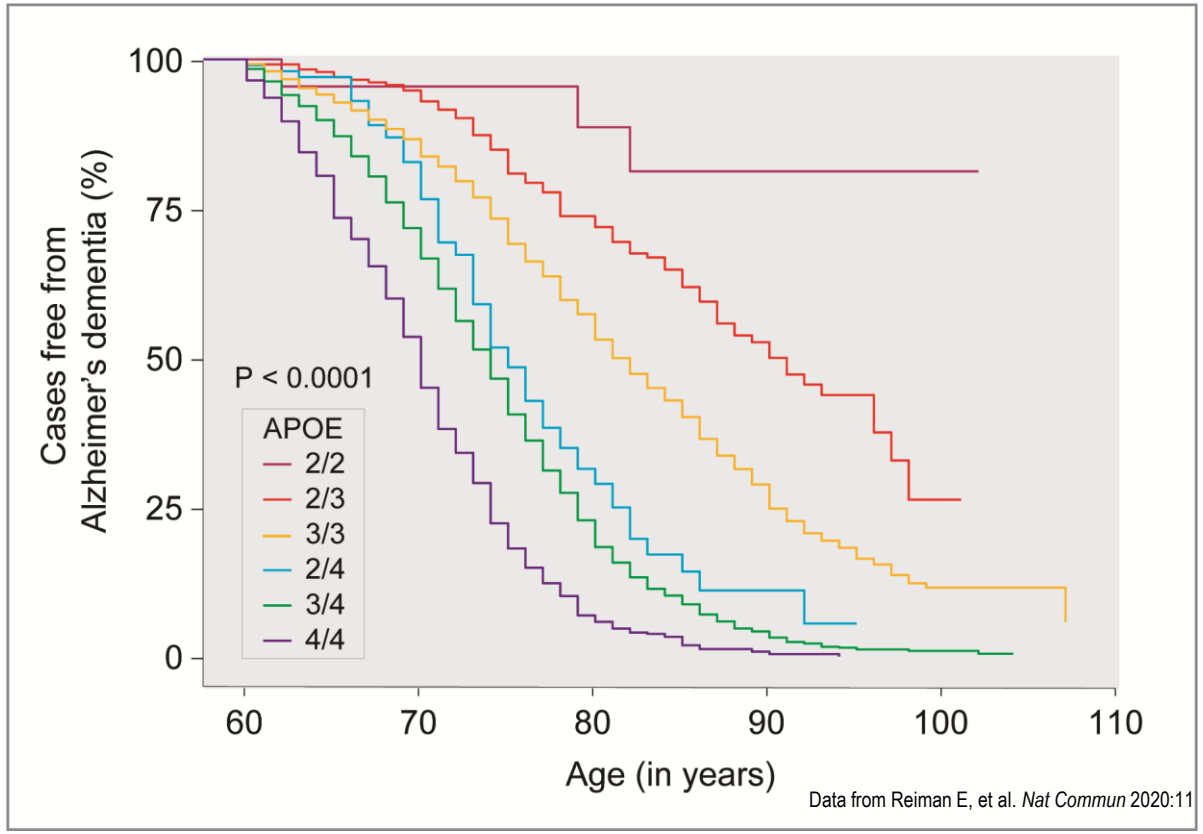
APOE ε4 allele increases the risk of developing AD, is associated with amyloid accumulation, cerebral amyloid angiopathy risk, and an earlier age of AD onset

Pleiotropic roles of ApoE ε4



Data from Liu CC, et al. *Nat Rev Neurol* 2013;9(2):106-18

APOE ε4 genotype modifies age at AD onset



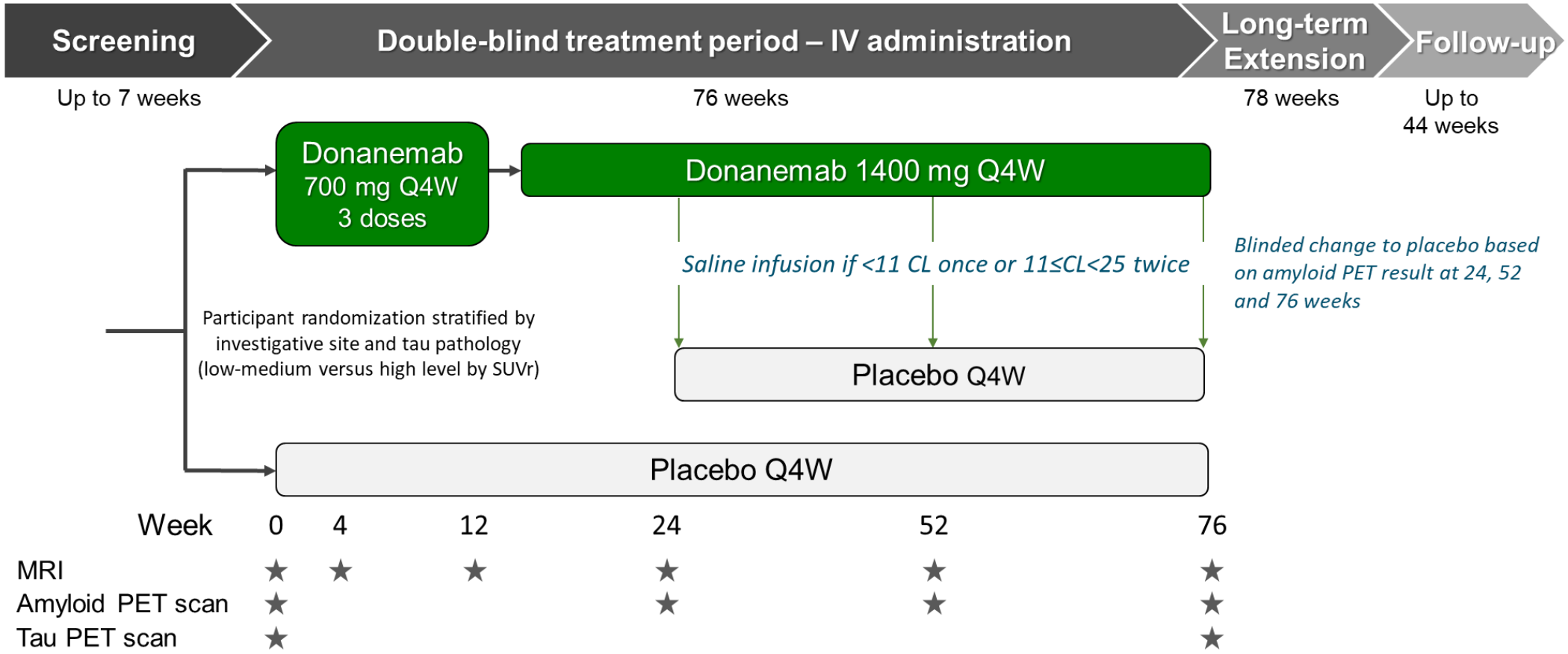
Data from Reiman E, et al. *Nat Commun* 2020:11

Question: is there differential efficacy of amyloid targeting therapies by *APOE ε4* carrier status and genotype?

Abbreviations: AD=Alzheimer's Disease; *APOE* ε4=apolipoprotein E ε4.

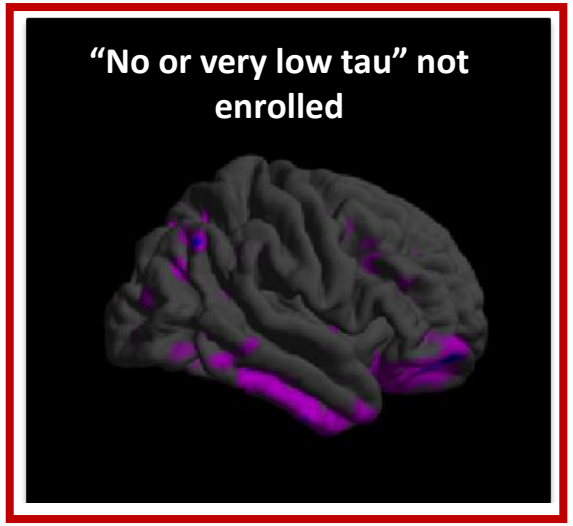
TRAILBLAZER-ALZ 2 Trial Design

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

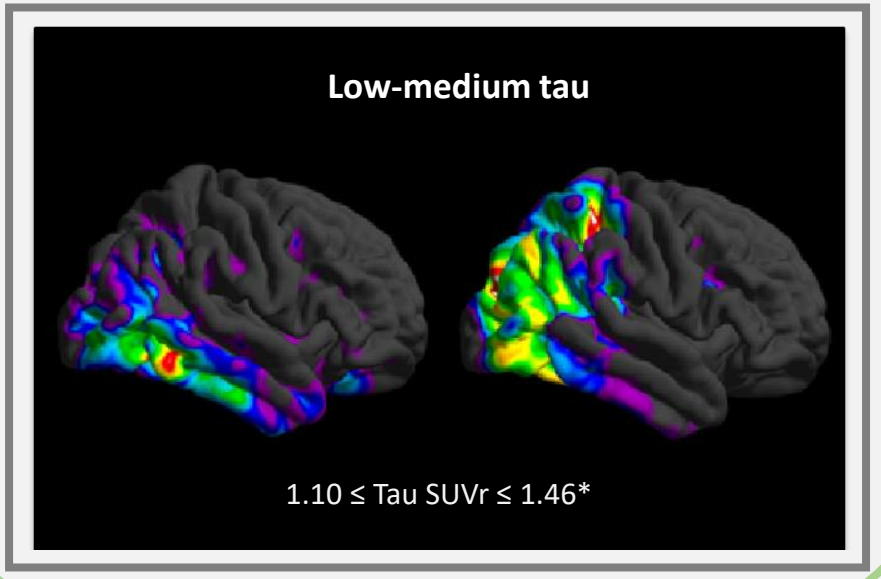


Abbreviations: AD=Alzheimer's Disease; CL=Centiloid unit; IV=intravenous; MRI=magnetic resonance imaging; PET=positron emission tomography; Q4W=every 4 weeks; SUVr=standardized uptake value ratio

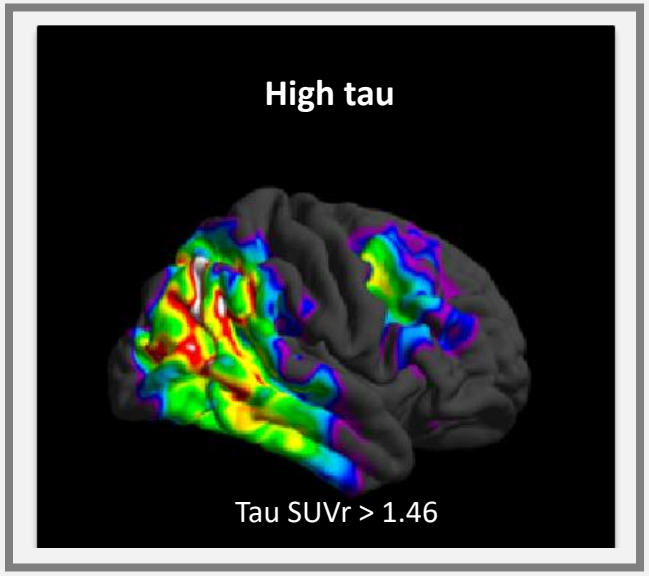
Enrolling participants based on tau pathology



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 overall 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

Demographics and key baseline measures by *APOE ε4* carrier status: balanced except carriers are younger

Low-medium tau population

Baseline demographics

Demographic	*APOE ε4* Carriers (N=848)	*APOE ε4* Noncarriers (N=330)	p-value
Sex, % Female	54.6%	55.2%	0.896
Age, mean	73.6	76.0	<0.001
Race, % Asian	6.0%	10.6%	0.016
% Black or AA	2.9%	2.7%	
% White	91.0%	86.4%	
% Other*	0%	0.3%	
Clinical Stage#, Mild AD	79.6%	82.1%	0.545
MCI	20.3%	17.9%	
AChEI and/or Memantine Use, Yes	57.3%	55.8%	0.647

Baseline scales & imaging

Scale, Mean (SD)	*APOE ε4* Carriers (N=848)	*APOE ε4* Noncarriers (N=330)	p-value
ADAS-Cog$_{13}$	27.4	28.0	0.271
ADCS-iADL	48.5	47.5	0.045
iADRS	106.2	104.5	0.061
MMSE	23.1	22.7	0.153
CDR-SB	3.7	3.8	0.271
Amyloid PET Centiloids	101.5	101.8	0.897
Tau PET MUBADA SUVr	1.22	1.20	0.064
Whole Brain Volume (cm^3)	978.4	968.0	0.108

71.7% (421/588) donanemab and 72.3% (427/594) placebo in low-medium tau population were *APOE ε4* carriers

*Includes American Indian or Alaska Native. #Defined as clinical category by MMSE at screening: MCI >=27; mild AD 20-26). Abbreviations: AA=African American; AChEI=acetylcholinesterase inhibitors; AD=Alzheimer's Disease; ADAS-Cog$_{13}$=Alzheimer's Disease Assessment Scale-Cognitive subscale; 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; MUBADA=multi-block barycentric discriminant analysis; N=number of participants; PET=positron emission tomography; SUVr=standardized uptake value ratio

Demographics and key baseline measures by *APOE ε4* carrier status: balanced except carriers are younger

Overall population

Baseline demographics

Demographic	*APOE ε4* Carriers (N=1219)	*APOE ε4* Noncarriers (N=510)	p-value
Sex, % Female	57.2%	58.0%	0.749
Age, mean	72.6	73.9	<0.001
Race, % Asian	5.0%	8.4%	0.006
% Black or AA	2.5%	1.8%	
% White	92.4%	89.4%	
% Other*	0.1%	0.4%	
Clinical Stage#, Mild AD	82.9%	85.3%	0.474
MCI	17.0%	14.7%	
AChEI and/or Memantine Use, Yes	60.4%	62.2%	0.517

Baseline scales & imaging

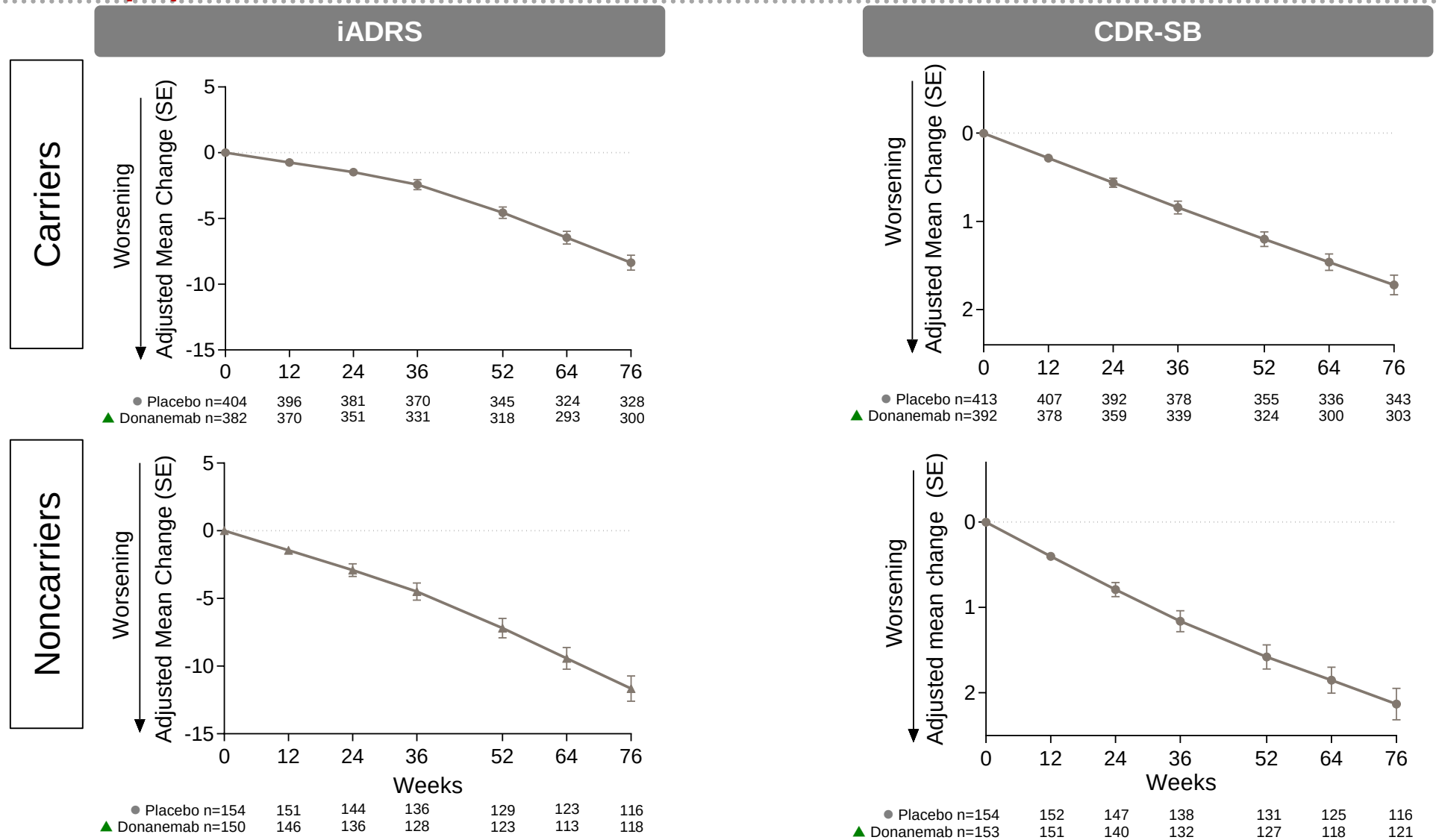
Scale, Mean (SD)	*APOE ε4* Carriers (N=1219)	*APOE ε4* Noncarriers (N=510)	p-value
ADAS-Cog$_{13}$	28.9	29.2	0.521
ADCS-iADL	48.2	47.0	0.007
iADRS	104.3	102.9	0.056
MMSE	22.4	22.0	0.050
CDR-SB	3.9	4.1	0.059
Amyloid PET Centiloids	102.1	103.5	0.450
Tau PET MUBADA SUVr	1.34	1.36	0.051
Whole Brain Volume (cm^3)	976.4	964.5	0.024

69.8% (598/860) donanemab and 71.2% (621/876) placebo in the overall population were *APOE ε4* carriers

*Includes American Indian or Alaska Native and multiple. #Defined as clinical category by MMSE at screening: MCI >=27; mild AD 20-26). Abbreviations: AA=African American; AChEI=acetylcholinesterase inhibitors; AD=Alzheimer's Disease; ADAS-Cog$_{13}$=Alzheimer's Disease Assessment Scale-Cognitive subscale; ADCS-iADL=Alzheimer's Disease Cooperative Study–instrumental Activities of Daily Living; CDR-SB=Clinical Dementia Rating scale–Sum of Boxes; iADRS=Integrated Alzheimer's Disease Rating Scale; MMSE=Mini-Mental State Examination; MUBADA=multi-block barycentric discriminant analysis; N=number participants; PET=positron emission tomography; SUVr=standardized uptake value ratio

Donanemab slows clinical decline in *APOE ε4* carriers and noncarriers by similar % in TRAILBLAZER-ALZ 2; Placebo noncarriers decline faster than carriers

Low-medium tau population



**p<0.01, ***p<0.001. LS mean change from baseline, SE, 95% CI and p-value are derived using natural cubic spline model with 2 degree of freedom. The model included fixed effect of treatment, basis expansion terms (two terms), subgroup, subgroup-by-treatment interaction, and 3-way subgroup-by-treatment-by basis expansion interaction terms. The model was also adjusted for age at baseline, pooled investigator, baseline tau category, and baseline AChI/Memantine use. Abbreviations: iADRS=Integrated Alzheimer's Disease Rating Scale; CDR-SB=Clinical Dementia Rating–Sum of Boxes; n=number of participants

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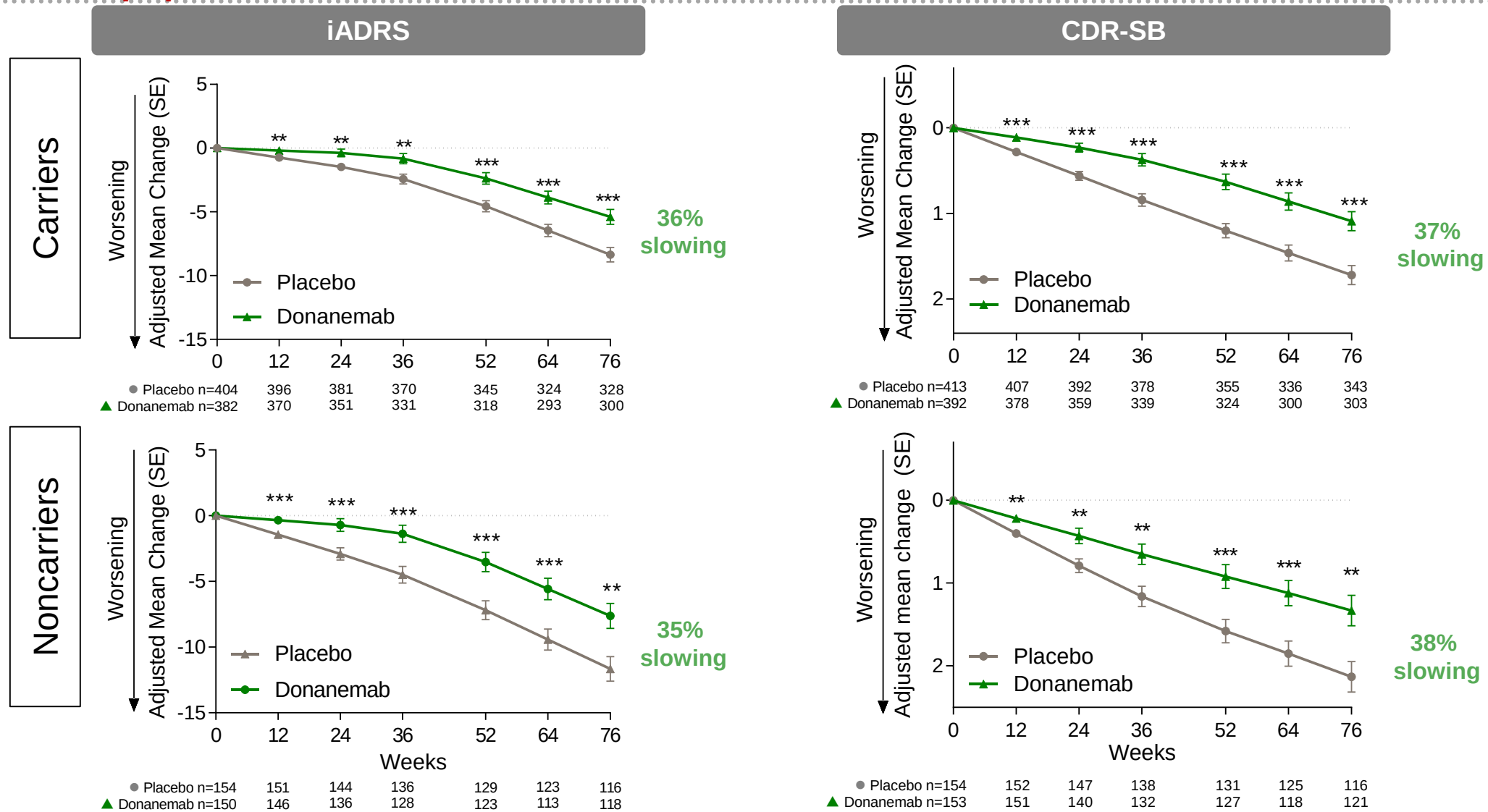

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Efficacy observed in *APOE ε4* carriers and noncarriers in TRAILBLAZER-ALZ 2 across scales in low-medium tau and overall populations

Carriers

Low-medium tau population

Scale	Treatment Difference	% Slowing	P-value
iADRS	2.97	**35.5**	<0.001
CDR-SB	-0.63	**36.6**	<0.001
ADAS-Cog$_{13}$	-1.56	**34.9**	<0.001
ADCS-iADL	1.57	**39.3**	0.004

Donanemab: N = ~305; Placebo: N = ~335 (at endpoint)

Overall population

Scale	Treatment Difference	% Slowing	P-value
iADRS	2.42	**20.5**	0.004
CDR-SB	-0.66	**29.8**	<0.001
ADAS-Cog$_{13}$	-1.10	**17.9**	0.016
ADCS-iADL	1.52	**27.4**	0.003

Donanemab: N = ~415; Placebo: N = ~480 (at endpoint)

Noncarriers

Scale	Treatment Difference	% Slowing	P-value
iADRS	4.03	**34.6**	0.003
CDR-SB	-0.80	**37.7**	0.002
ADAS-Cog$_{13}$	-1.46	**27.7**	0.040
ADCS-iADL	2.53	**40.9**	0.005

Donanemab: N = ~120; Placebo: N = ~115 (at endpoint)

Scale	Treatment Difference	% Slowing	P-value
iADRS	4.57	**28.0**	<0.001
CDR-SB	-0.76	**28.7**	<0.001
ADAS-Cog$_{13}$	-2.11	**25.3**	0.003
ADCS-iADL	2.37	**31.4**	0.003

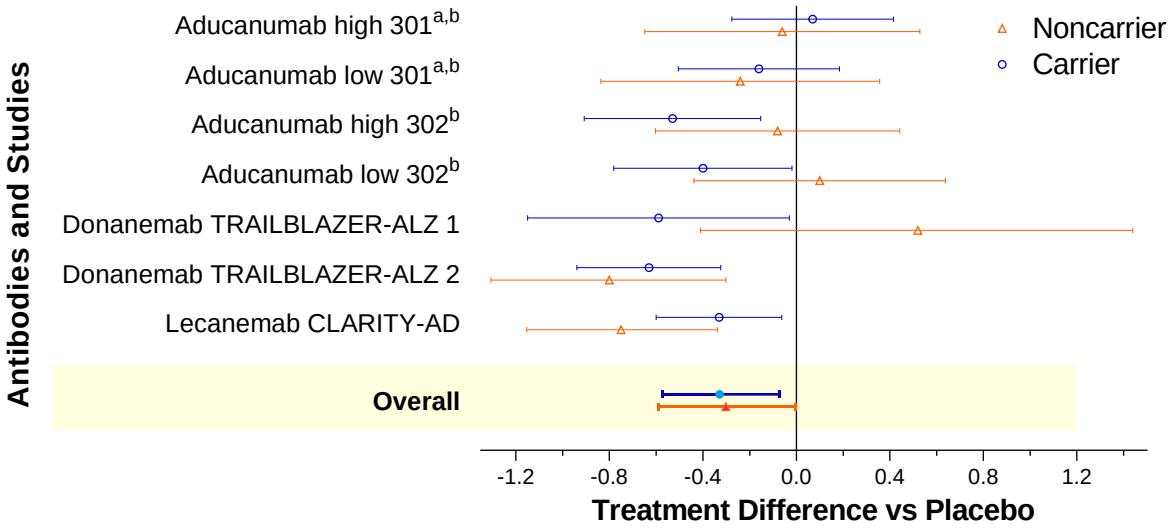
Donanemab: N = ~180; Placebo: N = ~185 (at endpoint)

% slowing significantly favors donanemab

% slowing donanemab vs placebo Abbreviations: iADRS=Integrated Alzheimer's Disease Rating Scale; CDR-SB=Clinical Dementia Rating–Sum of Boxes; ADAS-Cog$_{13}$=Alzheimer's Disease Assessment Scale-Cognitive subscale; ADCS-iADL=Alzheimer's Disease Cooperative Study–instrumental Activities of Daily Living; N=number participants.

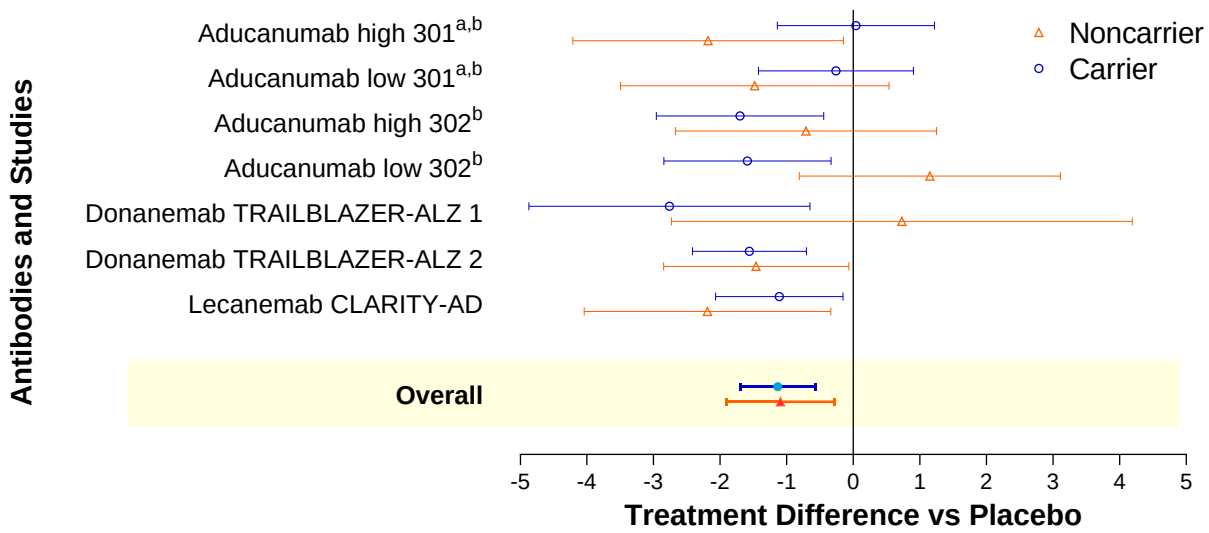
Amyloid targeting therapy efficacy across trials shows no difference in treatment effect between *APOE ε4* carriers and noncarriers

CDR-SB



Based on Overall Estimates	
Pr(TD of Carriers > Noncarriers)	0.585
Pr(TD of Carriers > 0)	0.990
Pr(TD of Noncarriers > 0)	0.976

ADAS-Cog



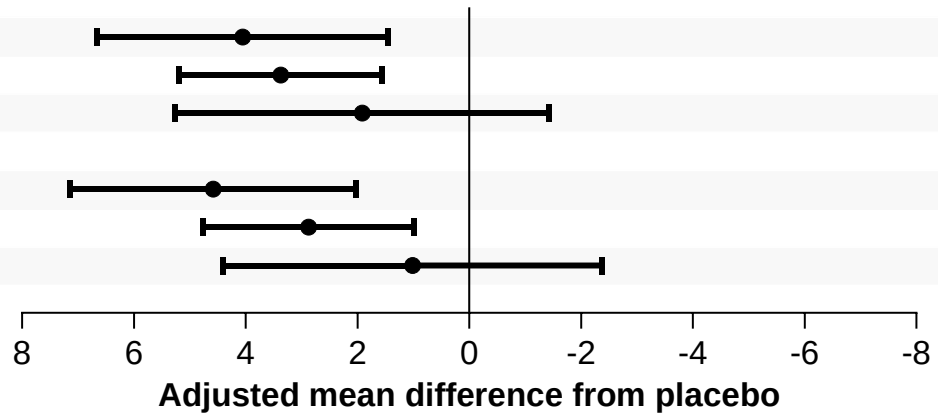
Based on Overall Estimates	
Pr(TD of Carriers > Noncarriers)	0.537
Pr(TD of Carriers > 0)	0.999
Pr(TD of Noncarriers > 0)	0.994

Adapted from Evans *et al*. Alzheimer's & Dementia. 2023 (updated with low-medium tau population TRAILBLAZER-ALZ 2 data).
Treatment differences relative to placebo and 95% confidence intervals for each individual plaque-lowering trial by *APOE* ε4 carrier status. The overall estimate and 95% credible interval by APOE ε4 carrier status are provided from Bayesian hierarchical model of all included trials. [a]Study 301 included for completeness. [b]Ns at month 18 for the placebo and treatment arms were estimated assuming the same dropout observed in the overall result for that study, dose, and endpoint.
Abbreviations: *APOE* ε4=apolipoprotein E ε4; ADAS-Cog=Alzheimer's Disease Assessment Scale–Cognitive subscale; CDR-SB=Clinical Dementia Rating–Sum of Boxes; Pr=probability; TD=treatment difference.

Smaller *APOE ε4/4* subgroup has treatment effect that favors donanemab treatment in TRAILBLAZER-ALZ 2

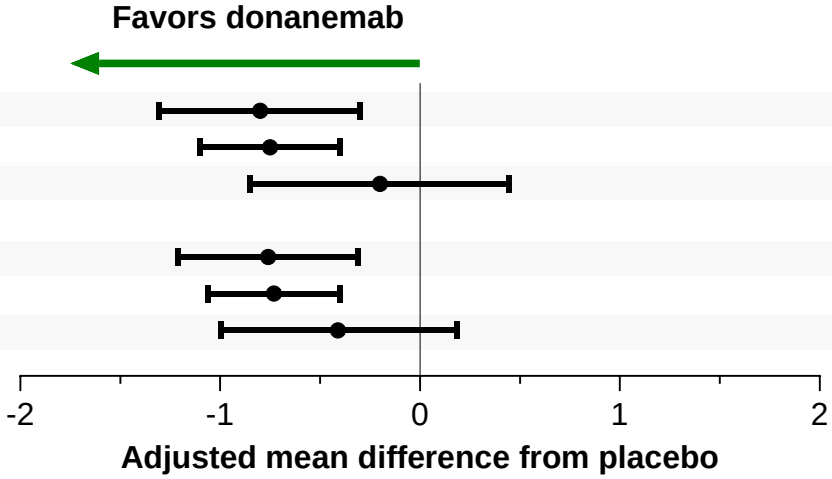
iADRS

APOE ε4 Genotype	N's (Placebo, Donanemab)	Adj. Mean Diff.	Percent slowing (95% CI)
Low-medium tau			
Noncarrier	(116, 118)	4.05	34.8 (11.82, 57.68)
Heterozygote	(243, 237)	3.37	37.4 (16.58, 58.13)
Homozygote	(85, 63)	1.91	30.4 (-23.88, 84.70)
Overall			
Noncarrier	(184, 177)	4.58	28.1 (12.18, 43.93)
Heterozygote	(350, 312)	2.87	23.8 (7.92, 39.67)
Homozygote	(119, 94)	1.01	9.3 (-21.89, 40.44)



CDR-SB

APOE ε4 Genotype	N's (Placebo, Donanemab	Adj. Mean Diff.	Percent slowing (95% CI)
Low-medium tau			
Noncarrier	(116, 121)	-0.80	37.7 (13.25, 62.25)
Heterozygote	(255, 241)	-0.75	43.3 (22.28, 64.22)
Homozygote	(88, 62)	-0.20	11.9 (-26.51, 50.32)
Overall			
Noncarrier	(184, 181)	-0.76	28.7 (11.25, 46.14)
Heterozygote	(365, 320)	-0.73	33.6 (18.13, 49.09)
Homozygote	(123, 97)	-0.41	17.7 (-8.13, 43.62)



Adapted from Sims JR, *et al.* JAMA. 2023

Abbreviations: *APOE* ε4=apolipoprotein E ε4; CDR-SB=Clinical Dementia Rating–Sum of Boxes; CI=confidence interval; iADRS=Integrated Alzheimer's Disease Rating Scale; N=number of participants

Substantial amyloid reduction across *APOE ε4* genotypes in TRAILBLAZER-ALZ 2

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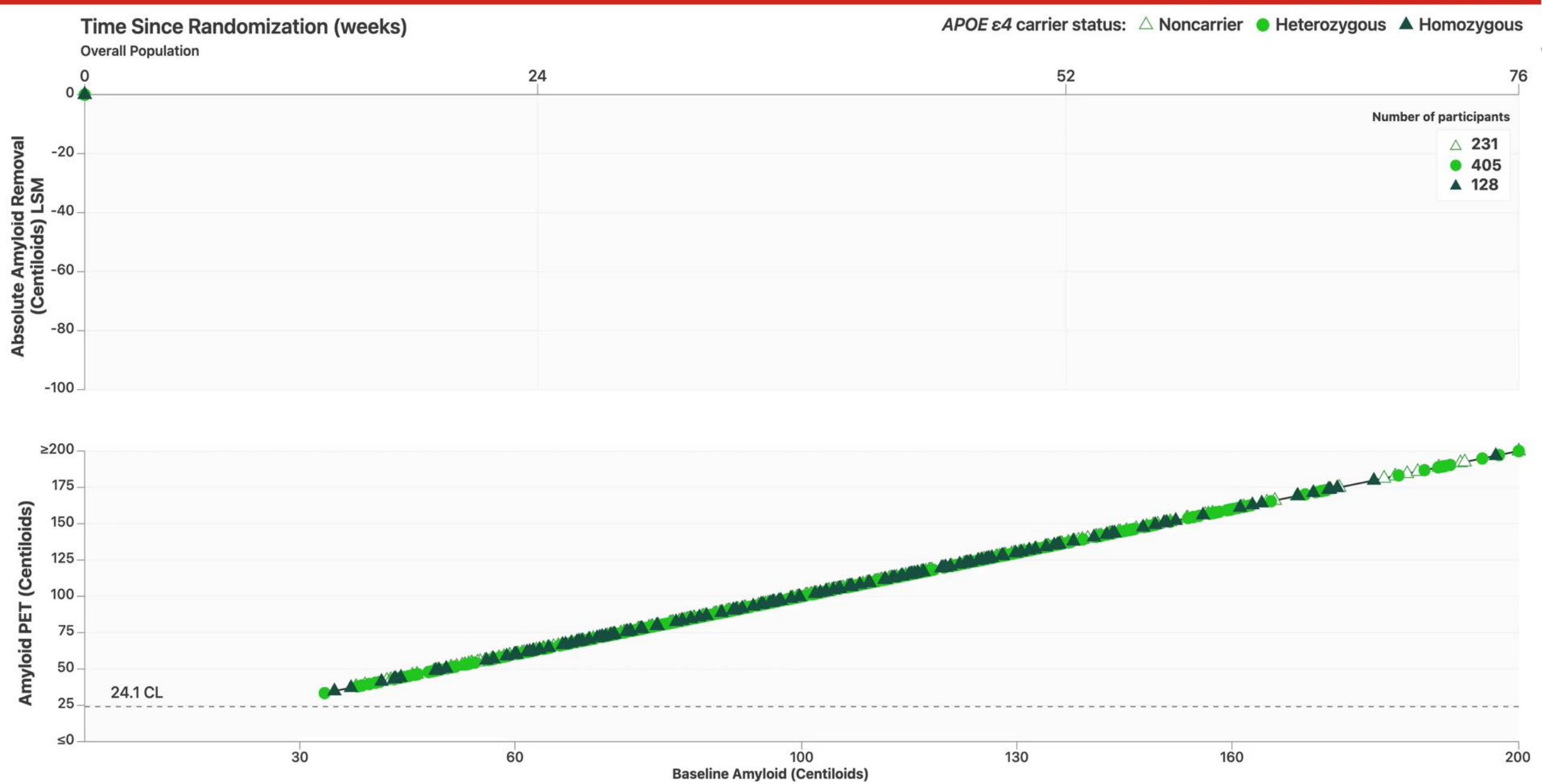
Substantial amyloid reduction across *APOE ε4* genotypes in TRAILBLAZER-ALZ 2

— Baseline Reference LSM = Least Squares Mean



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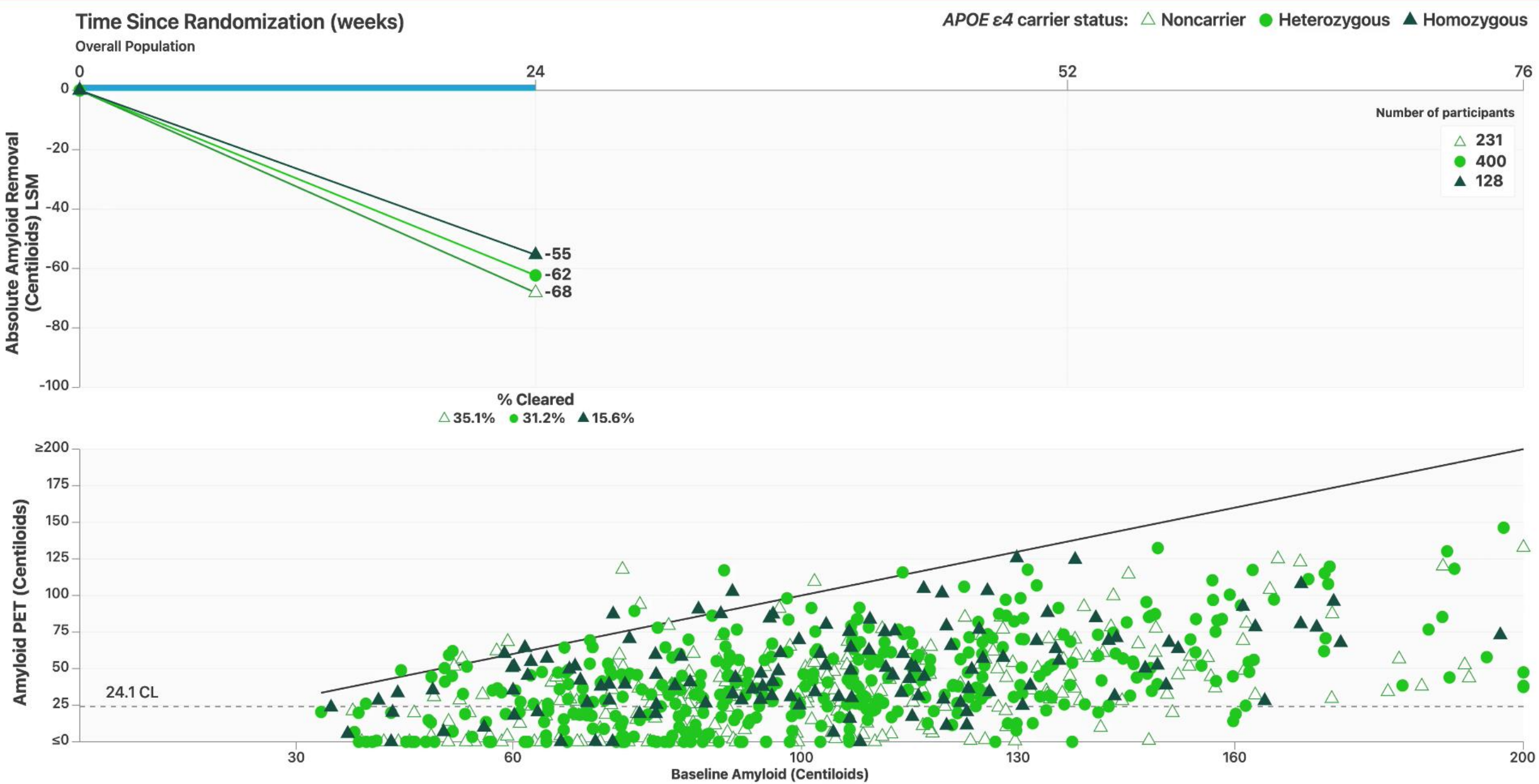

Substantial amyloid reduction across *APOE ε4* genotypes in TRAILBLAZER-ALZ 2

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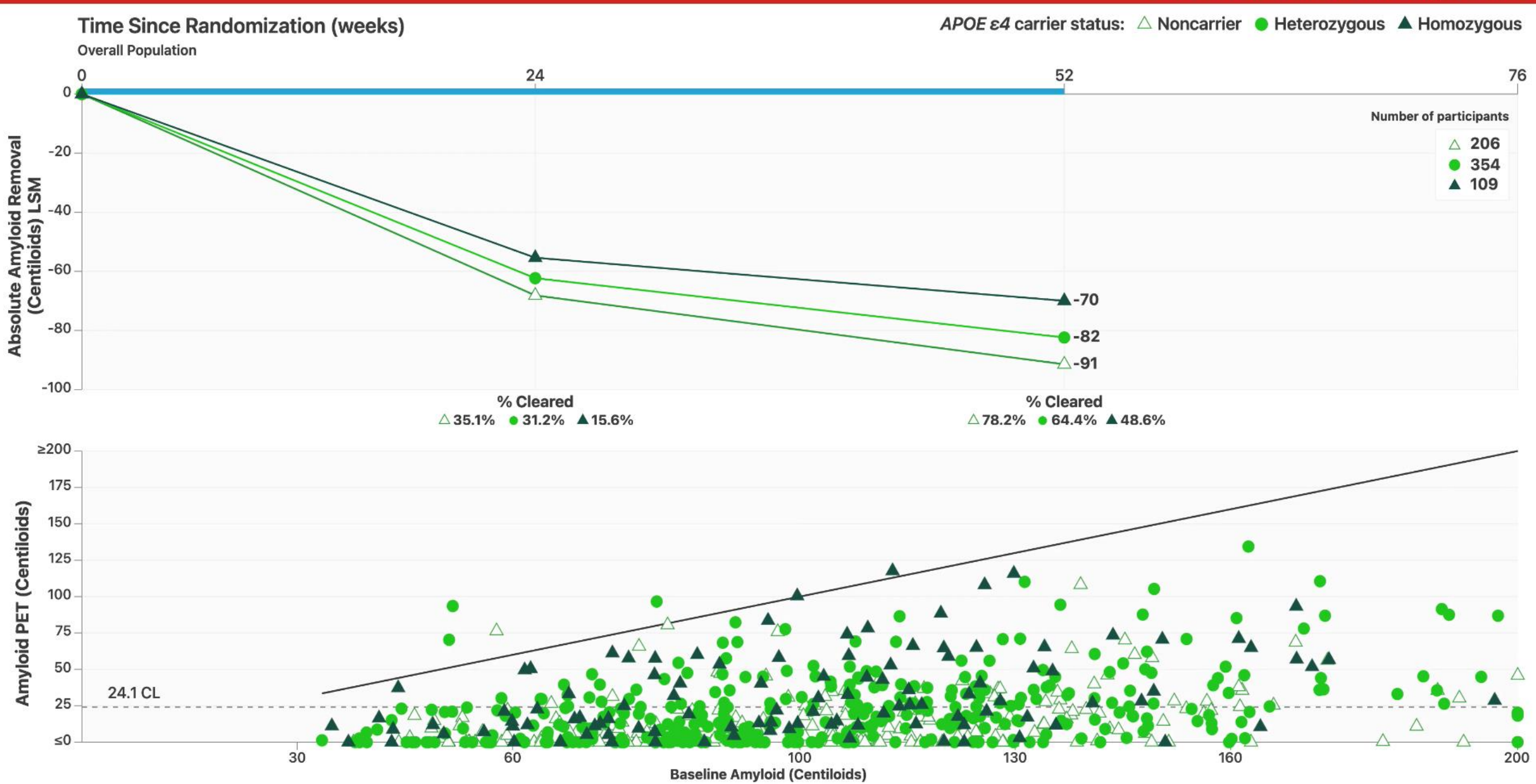

Substantial amyloid reduction across *APOE ε4* genotypes in TRAILBLAZER-ALZ 2

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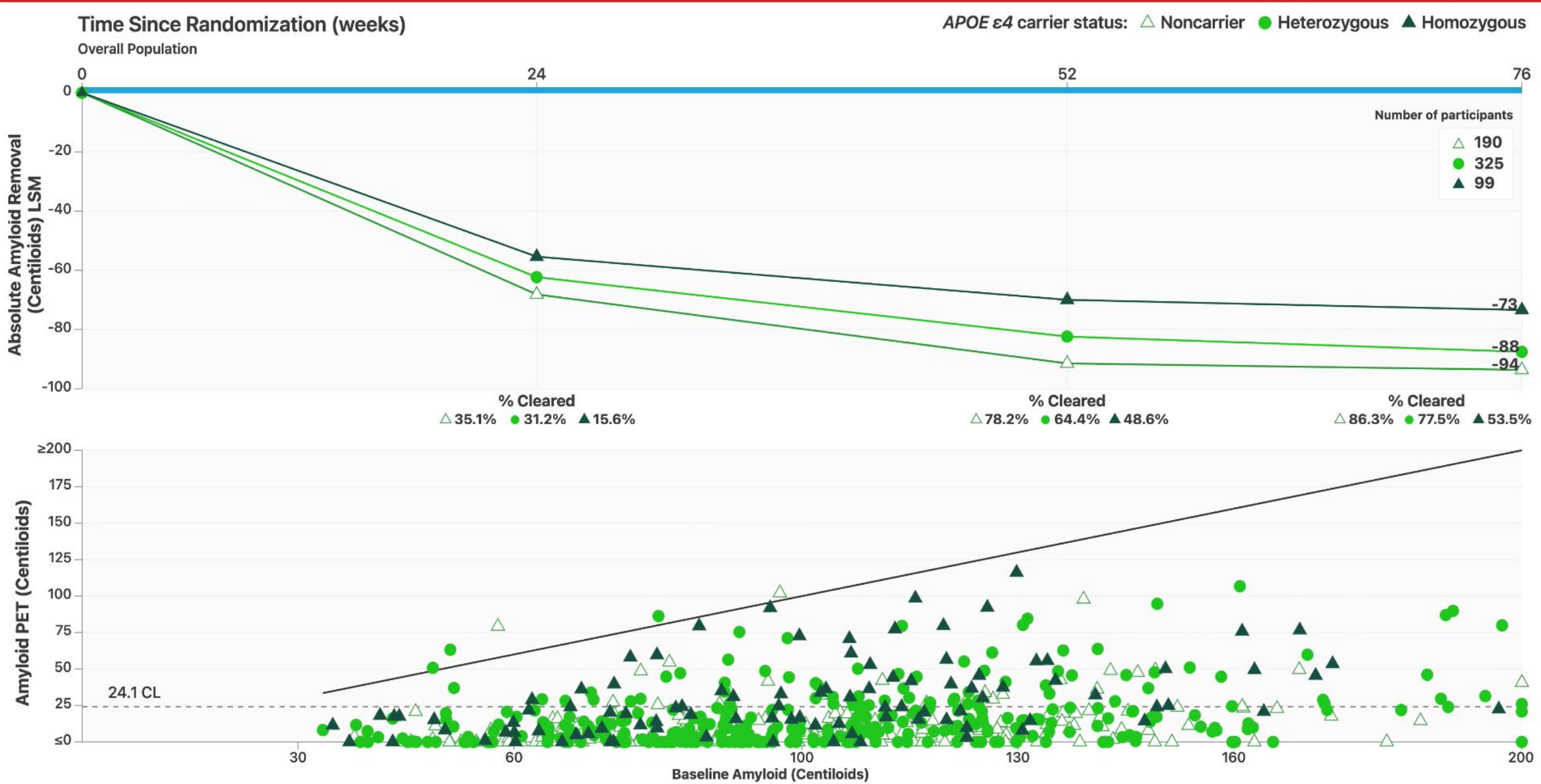
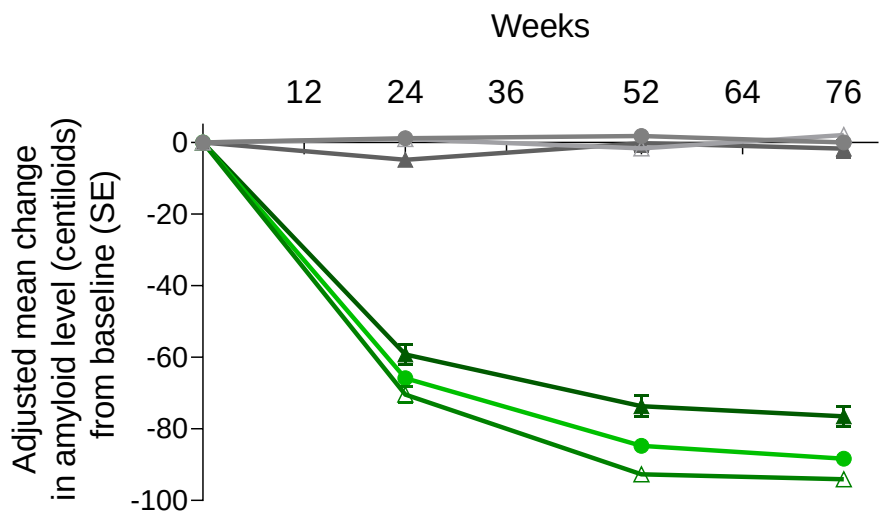


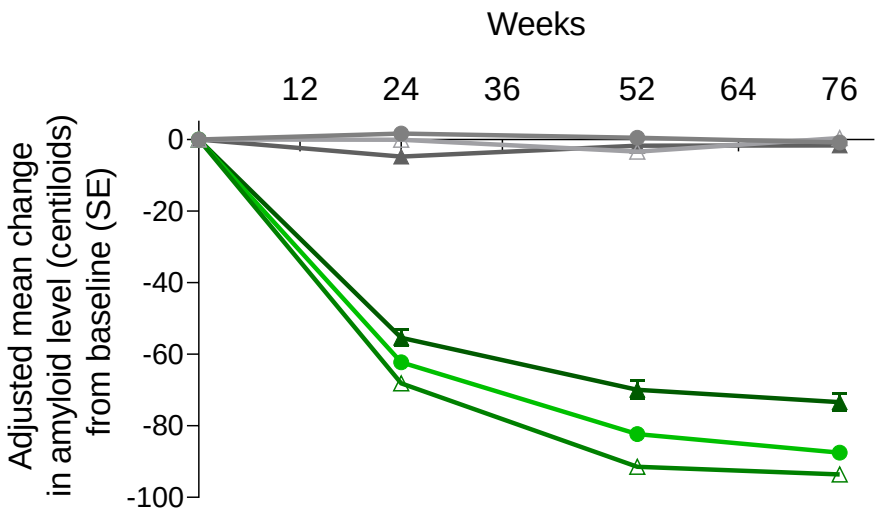
Substantial amyloid reduction across *APOE ε4* genotypes in TRAILBLAZER-ALZ 2

Low-medium tau population



PBO Noncarrier	N=150	150	131	122
PBO Heterozygous carrier	N=308	305	277	258
PBO Homozgous carrier	N=98	97	90	90
Dona Noncarrier	N=147	147	132	125
Dona Heterozygous carrier	N=296	292	259	243
Dona Homozgous carrier	N=82	82	72	65

Overall population



PBO Noncarrier	N=228	227	207	193
PBO Heterozygous carrier	N=442	437	395	371
PBO Homozgous carrier	N=142	141	127	126
Dona Noncarrier	N=231	231	206	190
Dona Heterozygous carrier	N=405	400	354	325
Dona Homozgous carrier	N=128	128	109	99

- Note treatment pauses due to ARIA are highest in E4 homozygotes. There was 13% less cumulative serum exposure at week 24 in E4 homozygotes vs noncarriers.
- Exposure-plaque model analyses of the current dataset do not find *APOE ε4* genotype to be a significant covariate on amyloid plaque reduction

Abbreviations: ARIA=amyloid-related imaging abnormalities; *APOE* ε4=apolipoprotein E ε4; PBO=placebo; Dona=donanemab; N=number of participants.

Conclusions

- TRAILBLAZER-ALZ 2 demonstrated efficacy of donanemab in *APOE ε4* heterozygous and homozygous carriers and in noncarriers
  - Homozygous *APOE ε4* carriers had numerically smaller treatment effects than heterozygotes or noncarriers but had the smallest sample size, differences in baseline demographics, more dose pauses, and fewer participants reaching amyloid clearance threshold by 24 weeks
- Mean amyloid clearance was robust among all donanemab-treated participant groups
- Noncarriers decline faster than carriers on clinical scales in amyloid selected early symptomatic AD populations[1]
- Differences in ARIA by *APOE ε4* genotype reviewed previously in Sims *et al.* JAMA. 2023[2]
- Aggregate data across amyloid targeting therapy trials with significant plaque lowering shows similar clinical efficacy in carriers and noncarriers

1. Evans *et al*. Alzheimer's & Dementia 2023; 2. Sims JR, et al. JAMA. 2023
Abbreviations: AD=Alzheimer's Disease; *APOE* ε4=apolipoprotein E ε4; ARIA=amyloid-related imaging abnormalities