Subgroup Analyses of the Plasma P-tau^{181} Population From EMERGE/ENGAGE, Phase 3 Clinical Trials Evaluating Aducanumab in Early Alzheimer's Disease

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AD/PD™ 2022 International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders

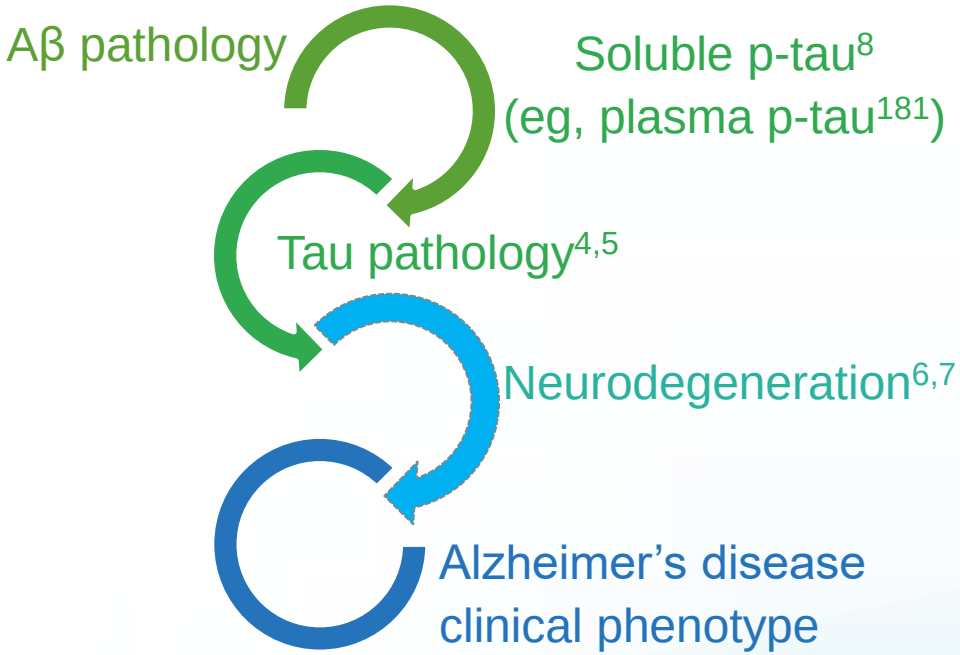
March 15-20, 2022 | Barcelona, Spain

Disclosures

- OH has acquired research support (for the institution) from AVID Radiopharmaceuticals, Biogen, Eli Lilly, Eisai, GE Healthcare, Pfizer, and Roche. In the past 2 years, he has received consultancy/speaker fees from AC Immune, Alzpath, Biogen, Cerveau, and Roche
- TC, KKM, and SBH are employees and shareholders of Biogen
- LN, RM, and RR were employees of Biogen at the time of this work and have since left the company
- Writing and editorial support for the preparation of this presentation was provided by MediTech Media (Atlanta, GA, USA); funding was provided by Biogen
- Aducanumab is approved for use in the following markets: the United States, the United Arab Emirates, and Qatar. In the rest of the world, it is an investigational drug. Its efficacy and safety have not been established in Spain

Plasma phosphorylated tau is a promising blood-based biomarker for Alzheimer's disease

- The International Working Group recommends that the diagnosis of Alzheimer's disease be made based on the presence of specific clinical phenotypes, as well as the biomarker evidence of Alzheimer's disease pathology[1]
- Alzheimer's disease pathology is characterized by accumulation of plaques comprising aggregated amyloid beta (Aβ) peptides and neurofibrillary tangles that contain phosphorylated tau (p-tau)[2,3]



Approximative ordering of Alzheimer's disease biomarker changes during the disease course

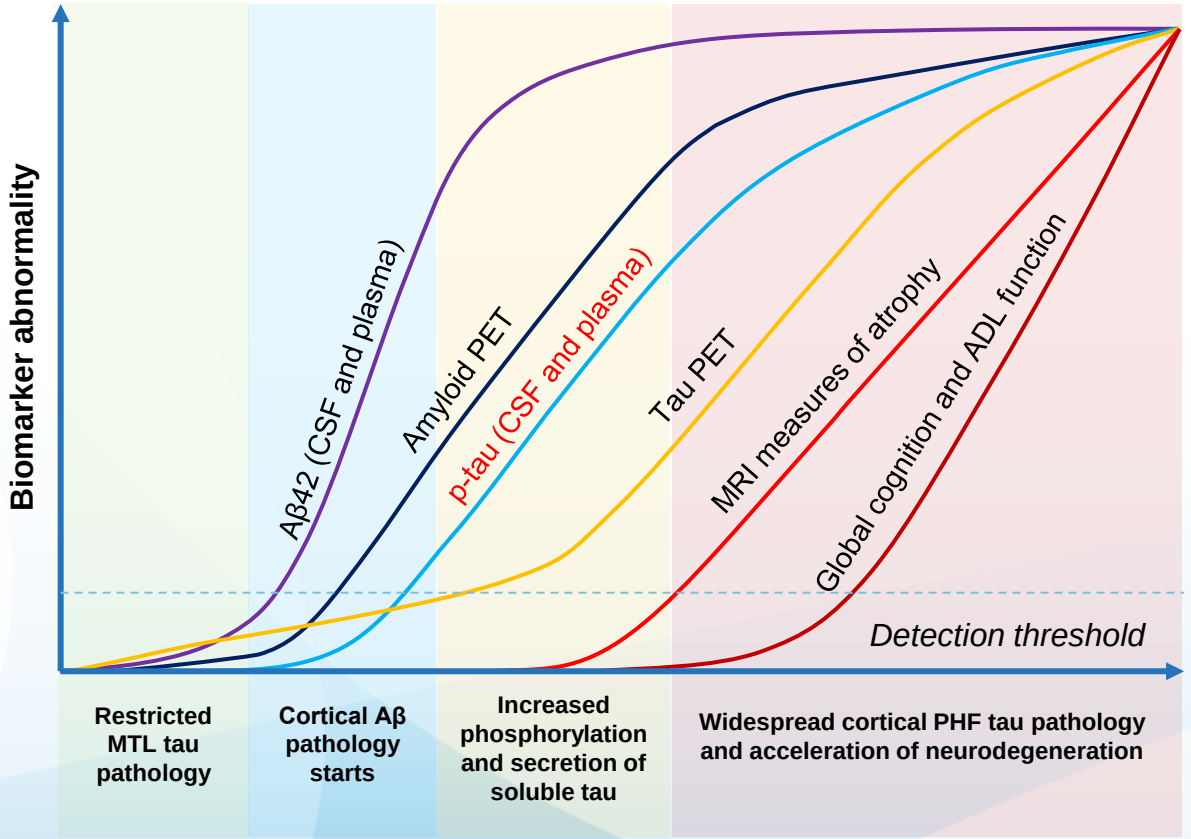


Figure adapted from Hansson O. *Nat Med*. 2021;27(6):954-963.[2]

Aβ, amyloid beta; ADL, activities of daily living; CSF, cerebrospinal fluid; MRI, magnetic resonance imaging; MTL, medial temporal lobe; PET, positron emission tomography; PHF, paired helical filaments; p-tau, phosphorylated tau.

1. Dubois B, et al. *Lancet Neurol*. 2021;20(6):484-496; 2. Alzheimer's Association. *Alzheimers Dement*. 2021;17(3):327-406; 3. Hansson O. *Nat Med*. 2021;27(6):954-963; 4. Mattsson-Carlgren N, et al. *Sci Adv*. 2020;6:eaaz2387; 5. Zheng WH, et al. *Neuroscience*. 2002;115(1):201-211; 6. Barthélemy NR, et al. *Nat Med*. 2020;26(3):398-407; 7. Gong CX, Iqbal K. *Curr Med Chem*. 2008;15(23):2321-2328; 8. Wang YL, et al. *Front Neurol*. 2021;12:695696.

EMERGE and ENGAGE were randomized, double-blind, placebo-controlled, Phase 3 studies of aducanumab[1-3]

- Aducanumab is a human immunoglobulin gamma 1 monoclonal antibody that selectively targets aggregated forms of Aβ, including soluble oligomers and insoluble fibrils[4-6]

	EMERGE[1,2]	ENGAGE[1,3]
	**Population**	• Early Alzheimer's disease (MCI due to AD + mild AD dementia) • Confirmed amyloid pathology
	**Doses**	• Two dosing regimens (low- and high-dose aducanumab) and placebo; randomized 1:1:1
	**Primary and secondary endpoints**	• Primary: CDR-SB at 18 months • Secondary: MMSE, ADAS-Cog 13, and ADCS-ADL-MCI
	**Substudies**	• Amyloid PET • Tau PET • CSF and plasma disease–related biomarkers

In EMERGE, treatment with high-dose aducanumab resulted in a statistically significant reduction compared with placebo on:[1]

- ✓ Prespecified primary and secondary endpoints
- ✓ Imaging and CSF biomarkers

ENGAGE did not meet its primary endpoint; however, participants who received adequate exposure to high-dose aducanumab had outcomes similar to those observed in EMERGE[1]

AD; Alzheimer's disease; ADAS-Cog 13, Alzheimer's Disease Assessment Scale–Cognitive Subscale (13 item); ADCS-ADL-MCI, Alzheimer's Disease Cooperative Study–Activities of Daily Living Inventory (mild cognitive impairment version); CDR-SB, Clinical Dementia Rating–Sum of Boxes; CSF, cerebrospinal fluid; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; PET, positron emission tomography.

1. Budd Haeberlein S, et al. Data presented at ADPD 2021; 2. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT02484547 Accessed March 8, 2022; 3. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT02477800 Accessed March 8, 2022; 4. Arndt J, et al. *Sci Rep.* 2018;8:64124; 5. Sevigny J, et al. *Nature*. 2016; 537:50−56; 6. Aduhelm. Prescribing information. Biogen, Inc.; 2021.

Investigating the effect of aducanumab treatment on plasma p-tau^{181} levels in EMERGE and ENGAGE

Objective

To investigate the effect of aducanumab treatment on plasma p-tau^{181} levels using data from the Phase 3 aducanumab trials—EMERGE and ENGAGE

- Participants with plasma samples at baseline and Week 78 were assessed
- A total of 6929 plasma samples from EMERGE and ENGAGE participants were analyzed using the Quanterix Simoa p-tau^{181} Advantage V2 kit at Frontage Laboratories's (Exton, PA) CLIA laboratory
- The inter-assay CV was 6.49% to 8.15% and the intra-assay CV was 8.30% to 9.21%

	EMERGE	ENGAGE	Total
Plasma p-tau^{181} analysis population, n	870	945	1815

CLIA, Clinical Laboratory Improvement Amendments; CV, coefficient of variability; p-tau, phosphorylated tau.

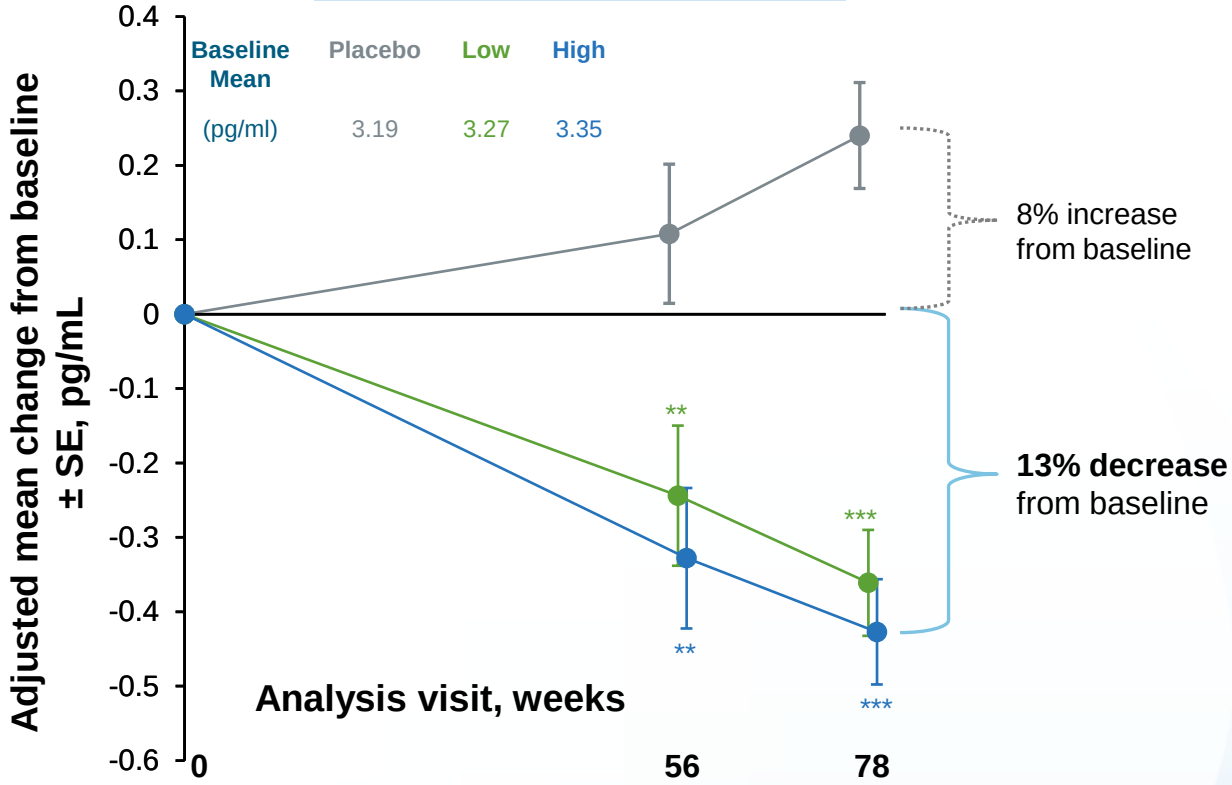
Baseline demographics and characteristics of AD were similar across groups in the plasma p-tau^{181} analysis subpopulation

	EMERGE			ENGAGE		
	Placebo (n=287)	Low dose (n=293)	High dose (n=290)	Placebo (n=333)	Low dose (n=331)	High dose (n=281)
Age, mean ± SD, years	70.6 ± 7.35	70.0 ± 7.53	70.3 ± 7.39	69.1 ± 7.76	70.2 ± 7.00	69.2 ± 7.92
Female, n (%)	147 (51.2)	135 (46.1)	145 (50.0)	171 (51.4)	176 (53.2)	150 (53.4)
Race, n (%)[a]						
Asian	10 (3.5)	7 (2.4)	10 (3.4)	24 (7.2)	30 (9.1)	21 (7.5)
Black or African American	0	1 (0.3)	2 (0.7)	4 (1.2)	1 (0.3)	2 (0.7)
White	244 (85.0)	252 (86.0)	232 (80.0)	263 (79.0)	255 (77.0)	214 (76.2)
Education, mean ± SD, years	14.7 ± 3.5	14.7 ± 3.4	14.7 ± 3.6	15.0 ± 3.6	14.7 ± 3.7	14.9 ± 3.8
Alzheimer's disease medications used, n (%)	154 (53.7)	158 (53.9)	156 (53.8)	184 (55.3)	199 (60.1)	170 (60.5)
ApoE ε4, n (%)						
Carrier	199 (69.3)	197 (67.2)	187 (64.5)	230 (69.1)	231 (69.8)	195 (69.4)
Noncarrier	88 (30.7)	96 (32.8)	103 (35.5)	102 (30.6)	100 (30.2)	86 (30.6)
Clinical stage, n (%)						
MCI due to AD	246 (85.7)	254 (86.7)	247 (85.2)	281 (84.4)	280 (84.6)	231 (82.2)
Mild AD dementia	41 (14.3)	39 (13.3)	43 (14.8)	52 (15.6)	51 (15.4)	50 (17.8)
Amyloid PET SUVR, mean composite ± SD	1.381 ± 0.180	1.399 ± 0.189	1.390 ± 0.193	1.376 ± 0.204	1.391 ± 0.186	1.412 ± 0.172
p-tau^{181}, mean ± SD, pg/mL	3.193 ± 1.347	3.265 ± 1.554	3.350 ± 2.617	3.181 ± 1.259	3.242 ± 1.320	3.114 ± 1.211

[a] Others not listed: American Indian or Alaska native, Native Hawaiian or other Pacific Islander, mot reported due to confidentiality regulations, or unknown.
AD, Alzheimer's disease; ApoE, apolipoprotein E; MCI, mild cognitive impairment; PET, positron emission tomography; pg/ml, picograms per milliliter; p-tau, phosphorylated tau; SD, standard deviation; SUVR, standardized uptake value ratio.

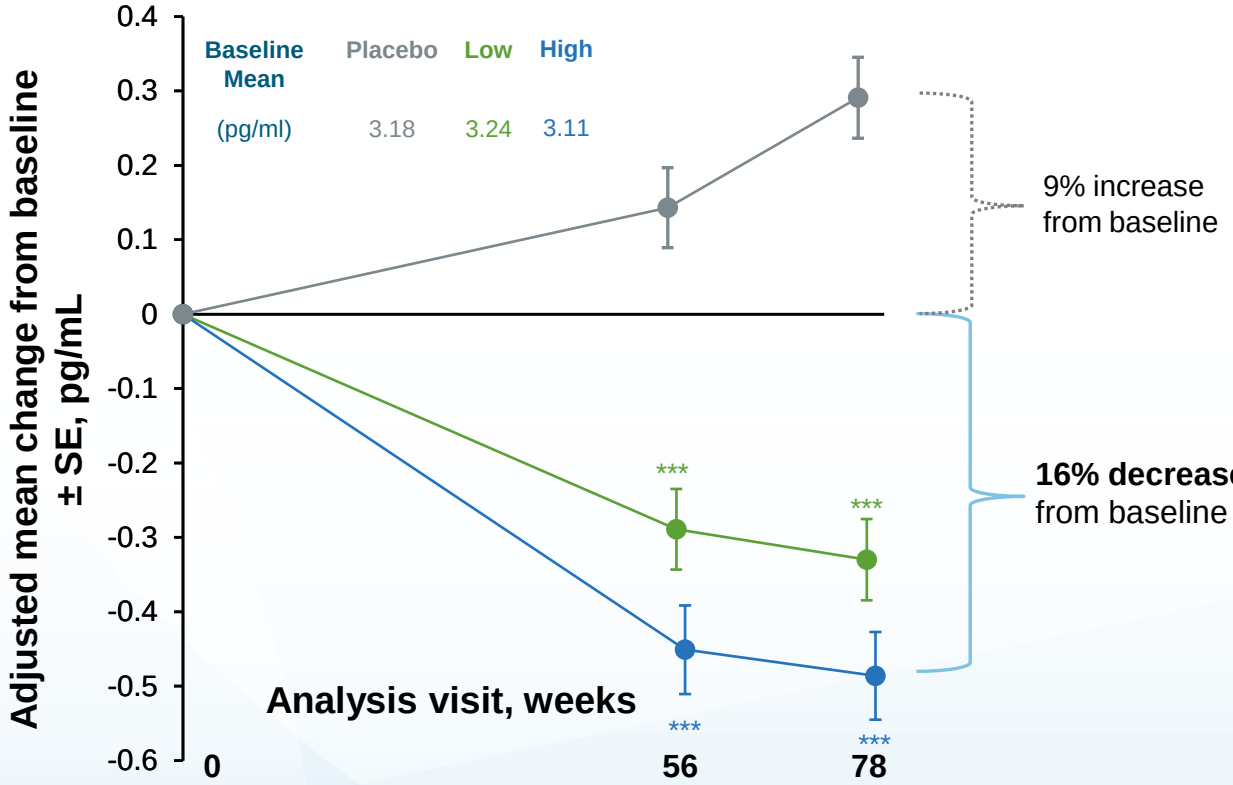
Aducanumab significantly lowered plasma p-tau^{181} levels in EMERGE and ENGAGE

EMERGE



	0	56	78
Placebo	287	177	273
Low dose	293	172	269
High dose	290	168	271

ENGAGE



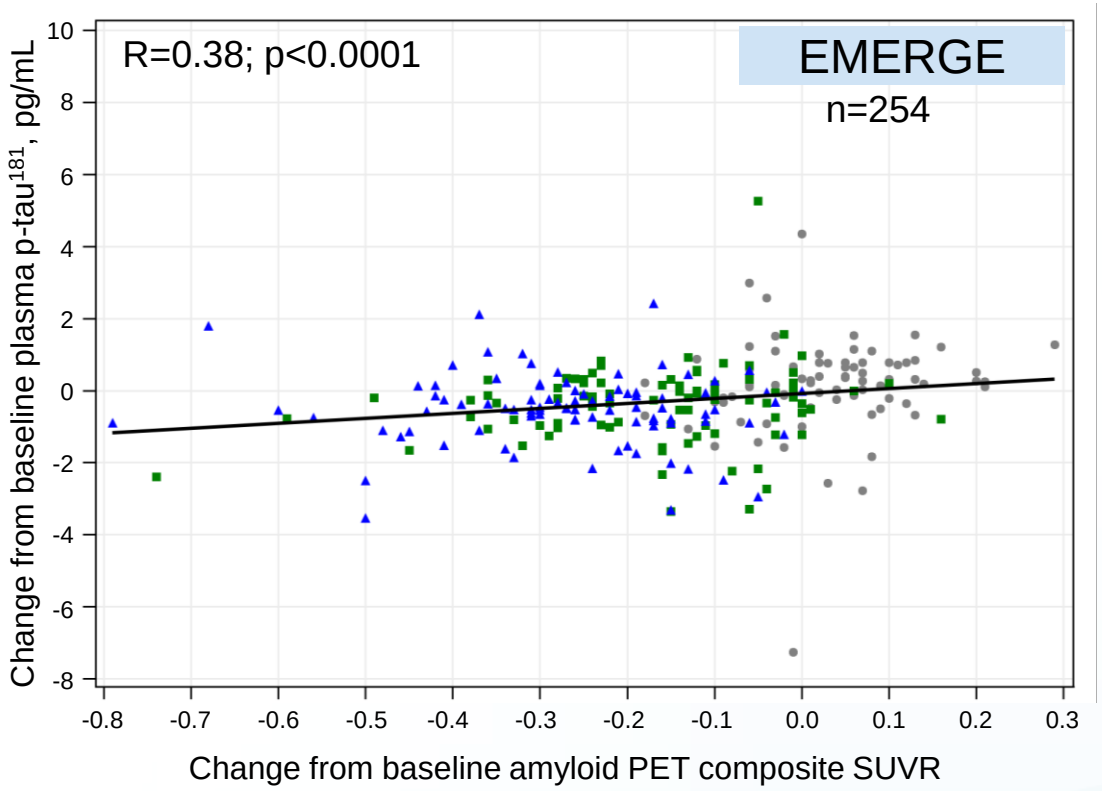
	0	56	78
Placebo	333	301	325
Low dose	331	299	322
High dose	281	242	274

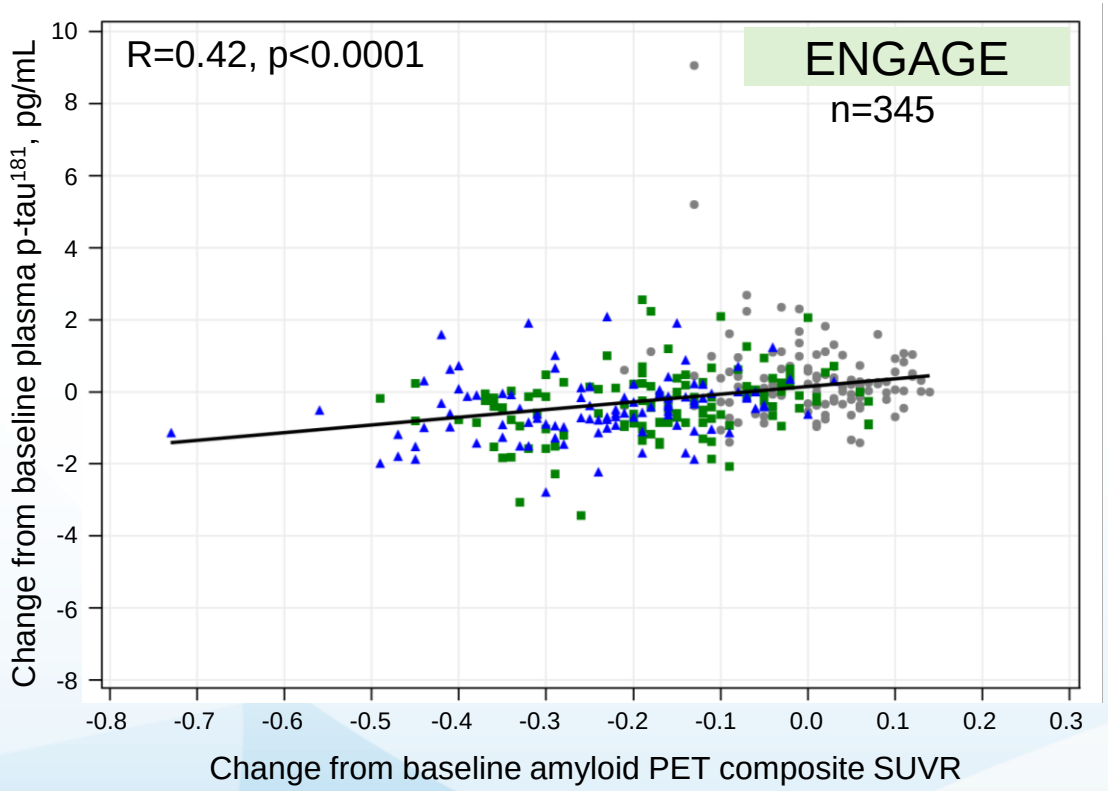
**p<0.01, ***p<0.001 compared with placebo (nominal). MMRM with change from baseline as the dependent variable and with fixed effects of treatment group, categorical visit, treatment-by-visit interaction, baseline value, baseline value by visit interaction, baseline age, and ApoE status.

ApoE, apolipoprotein E; MMRM, mixed model for repeated measures; pg/ml, picograms per milliliter; p-tau, phosphorylated tau; SE, standard error.

Change in plasma p-tau^{181} levels was correlated with change in amyloid PET SUVR at Week 78

Scatter plots of change from baseline plasma p-tau^{181} levels vs change from baseline florbetapir amyloid PET composite SUVR (reference region=cerebellum) at Week 78





● Placebo ■ Low-dose aducanumab ▲ High-dose aducanumab

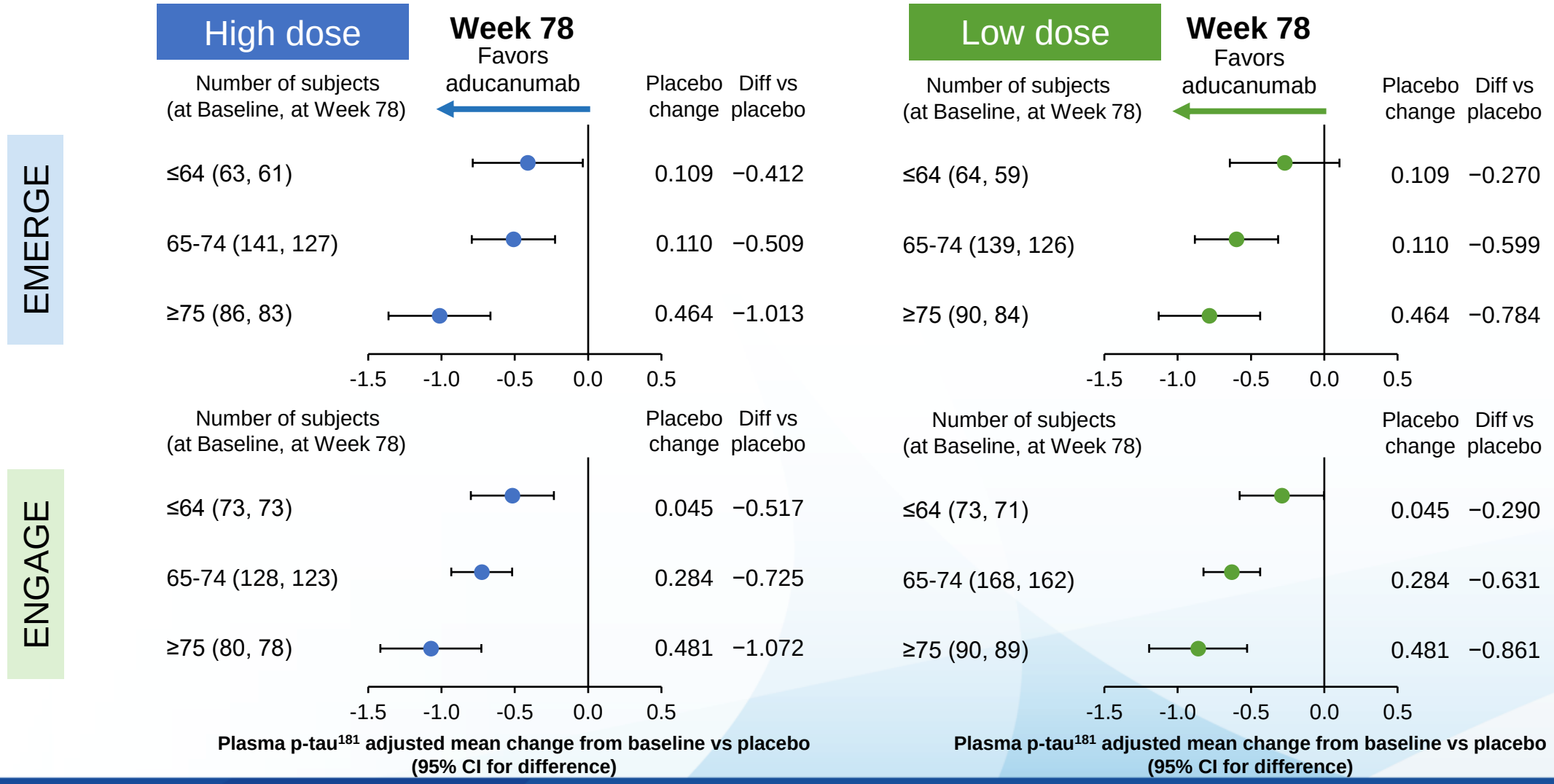
R: Spearman correlation adjusted for baseline p-tau, baseline amyloid PET, and age. Correlations calculated based on all arms.
PET, positron emission tomography; pg/ml, picograms per milliliter; p-tau, phosphorylated tau; SUVR, standardized uptake value ratio.

Aducanumab-induced reduction in plasma p-tau^{181} levels was associated with less clinical decline

Association between change in p-tau^{181} levels and efficacy at Week 78		Hypothesized correlation	Correlation (p value)	
			EMERGE (n=514–521)	ENGAGE (n=577–581)
p-tau^{181}	CDR-SB	Positive	**0.11** (0.0166)	**0.14** (0.0005)
	MMSE	Negative	**−0.21** (<0.0001)	**−0.15** (0.0002)
	ADAS-Cog 13	Positive	**0.17** (0.0001)	**0.15** (0.0002)
	ADCS-ADL-MCI	Negative	**−0.12** (0.0086)	**−0.14** (0.0010)

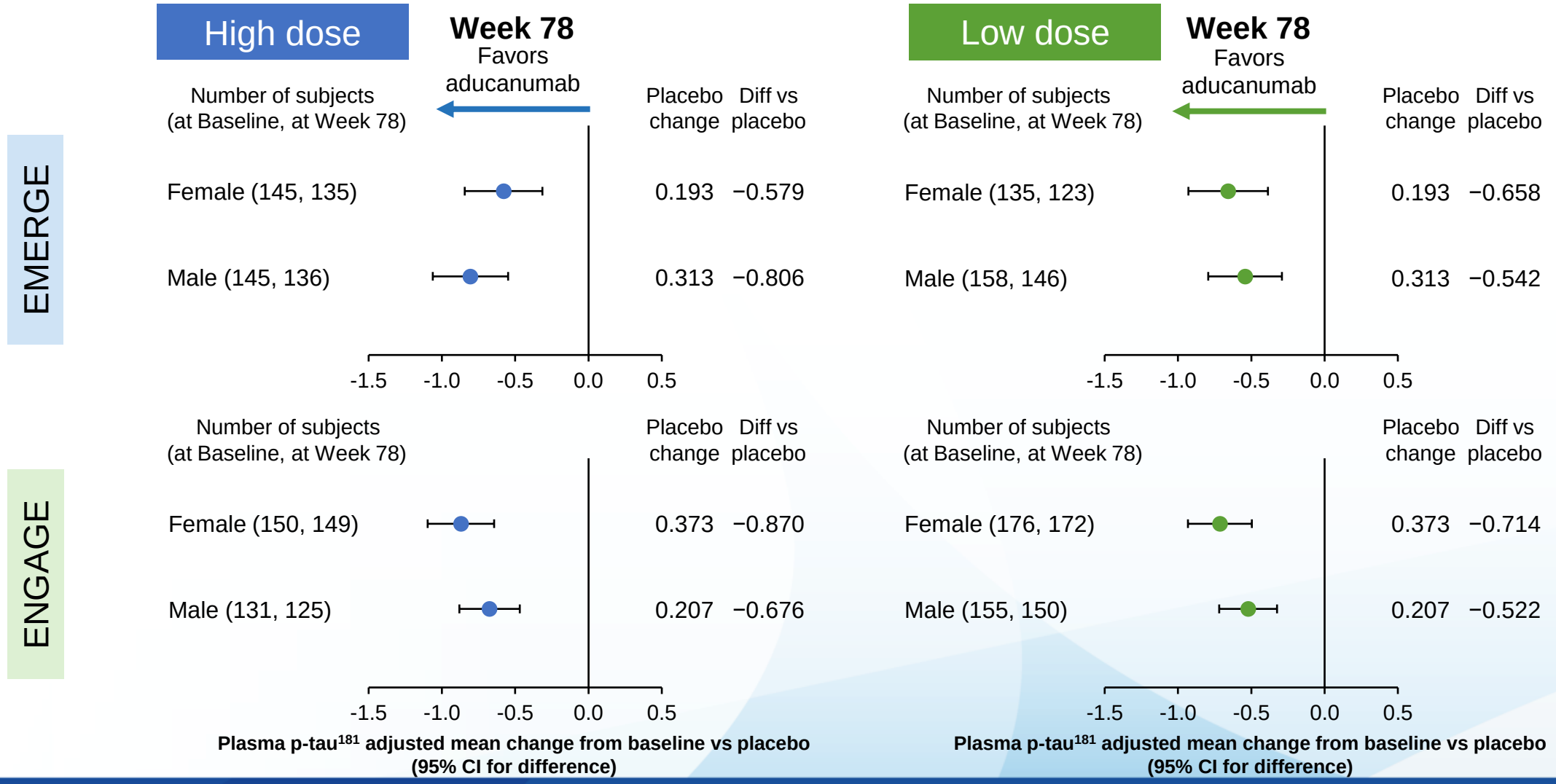
Correlations are partial Spearman correlations assessed in pooled low and high dose aducanumab-treated groups, adjusting for baseline p-tau, baseline clinical endpoint, and age.
ADAS-Cog 13, Alzheimer's Disease Assessment Scale–Cognitive Subscale (13 item); ADCS-ADL-MCI, Alzheimer's Disease Cooperative Study–Activities of Daily Living Inventory (mild cognitive impairment version); CDR-SB, Clinical Dementia Rating–Sum of Boxes; MMSE, Mini-Mental State Examination; p-tau, phosphorylated tau.

Reduction in plasma p-tau^{181} levels favored aducanumab vs placebo in prespecified subgroups: age



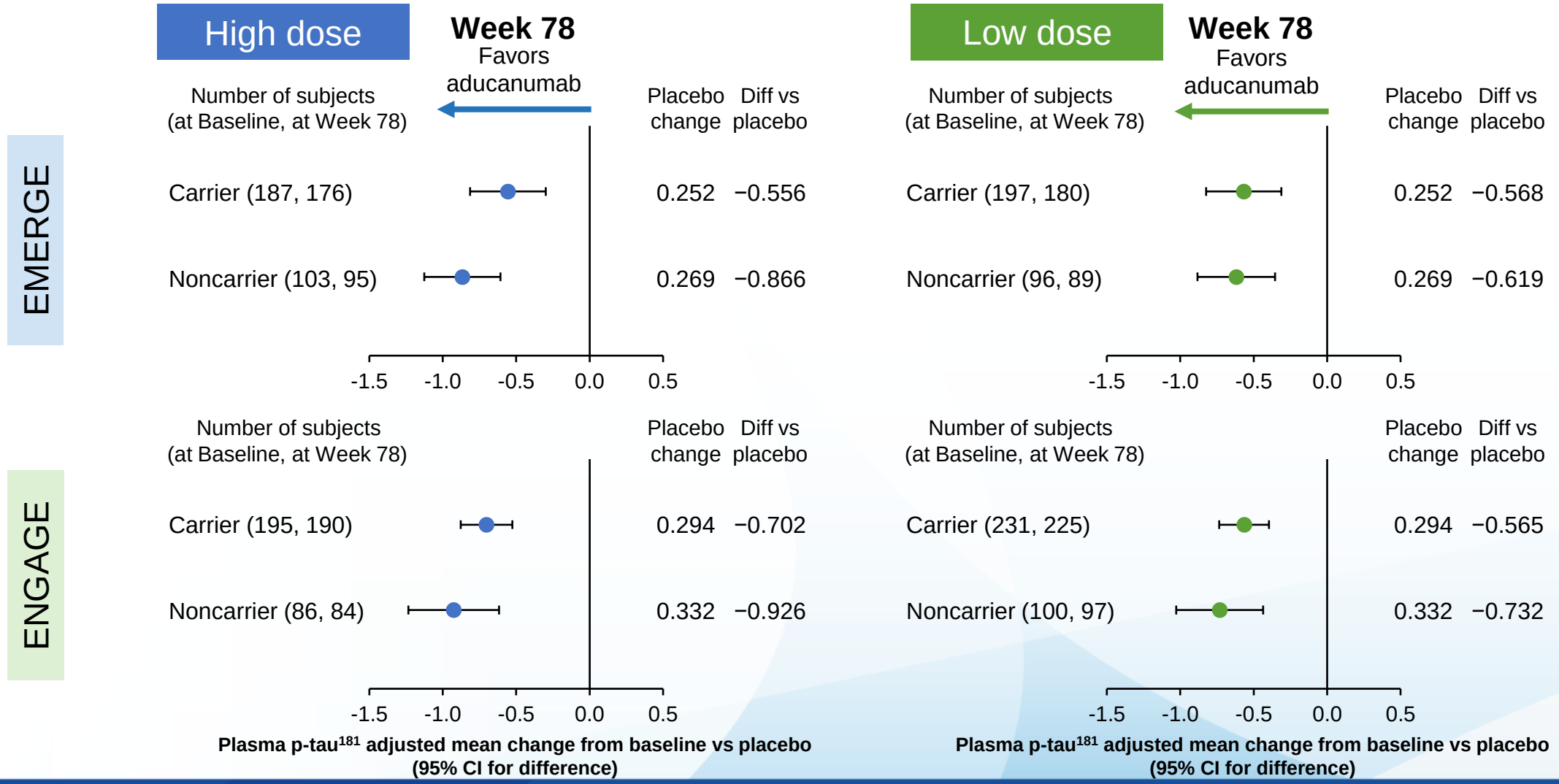
CI, confidence interval; p-tau, phosphorylated tau.

Reduction in plasma p-tau^{181} levels favored aducanumab vs placebo in prespecified subgroups: sex



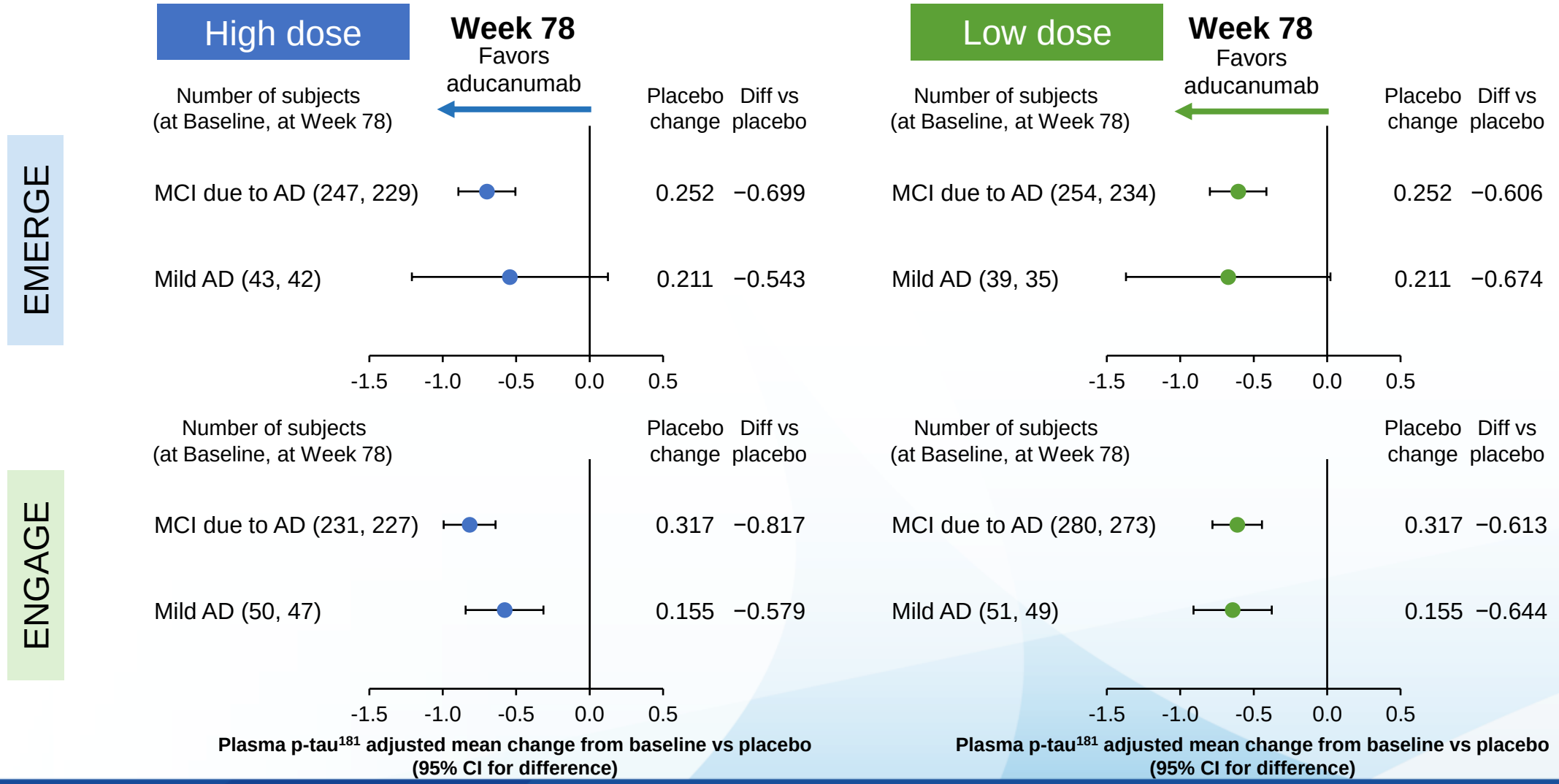
CI, confidence interval; p-tau, phosphorylated tau.

Reduction in plasma p-tau^{181} levels favored aducanumab vs placebo in prespecified subgroups: ApoE ε4 status



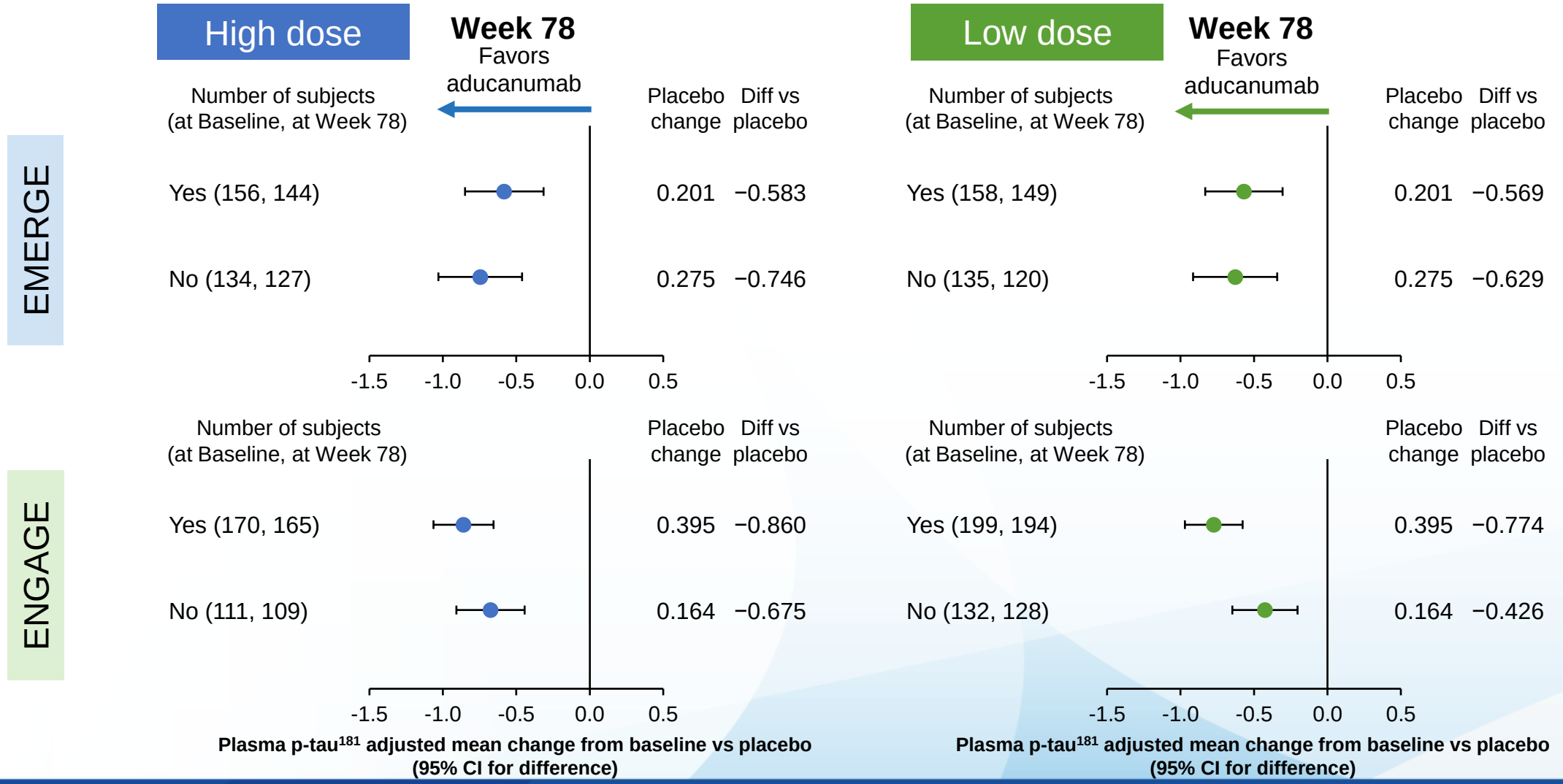
ApoE, apolipoprotein E; CI, confidence interval; p-tau, phosphorylated tau.

Reduction in plasma p-tau^{181} levels favored aducanumab vs placebo in prespecified subgroups: baseline clinical stage



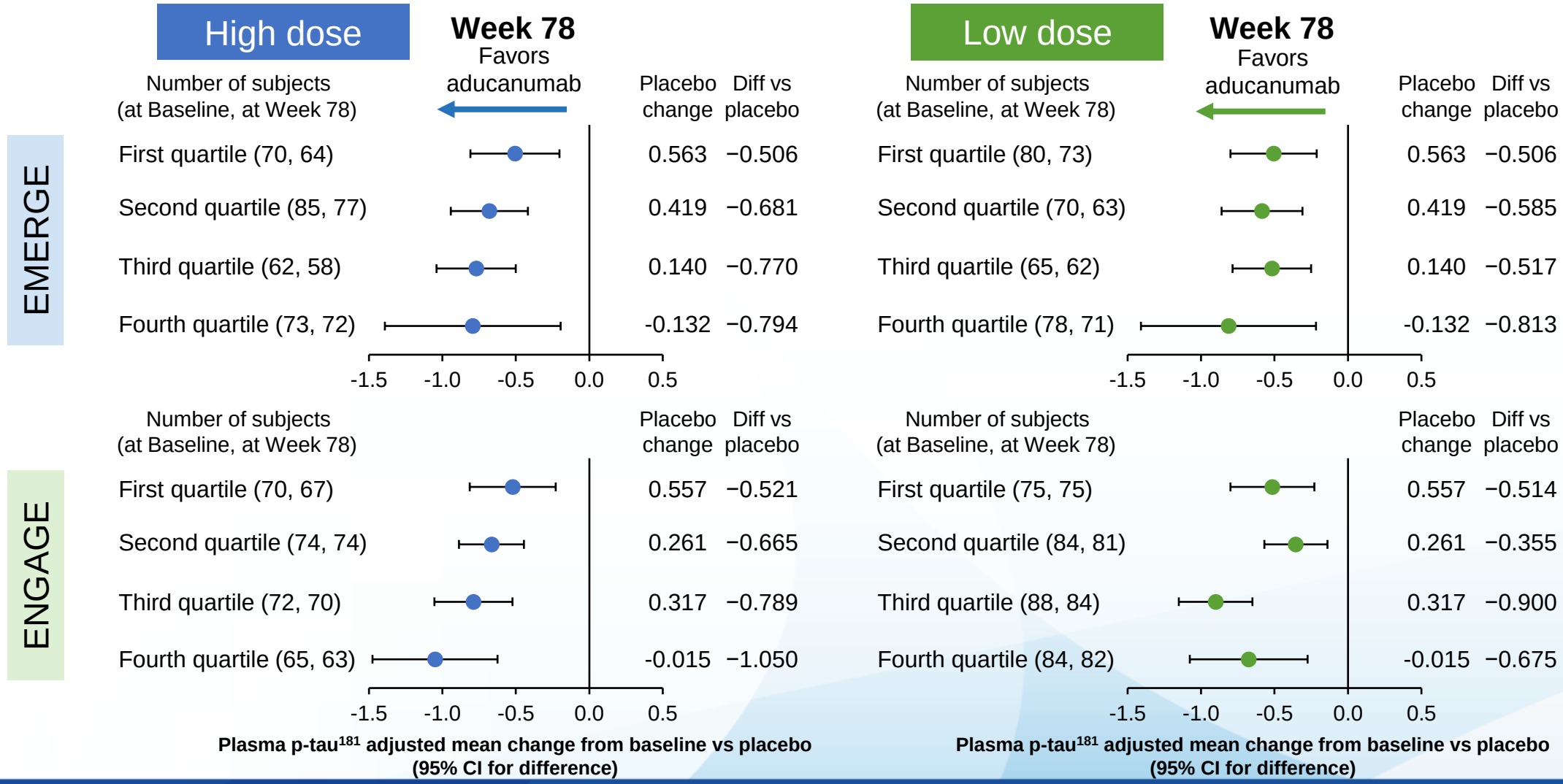
AD, Alzheimer's disease; CI, confidence interval; MCI, mild cognitive impairment; p-tau, phosphorylated tau.

Reduction in plasma p-tau^{181} levels favored aducanumab vs placebo in prespecified subgroups: baseline AD medication use



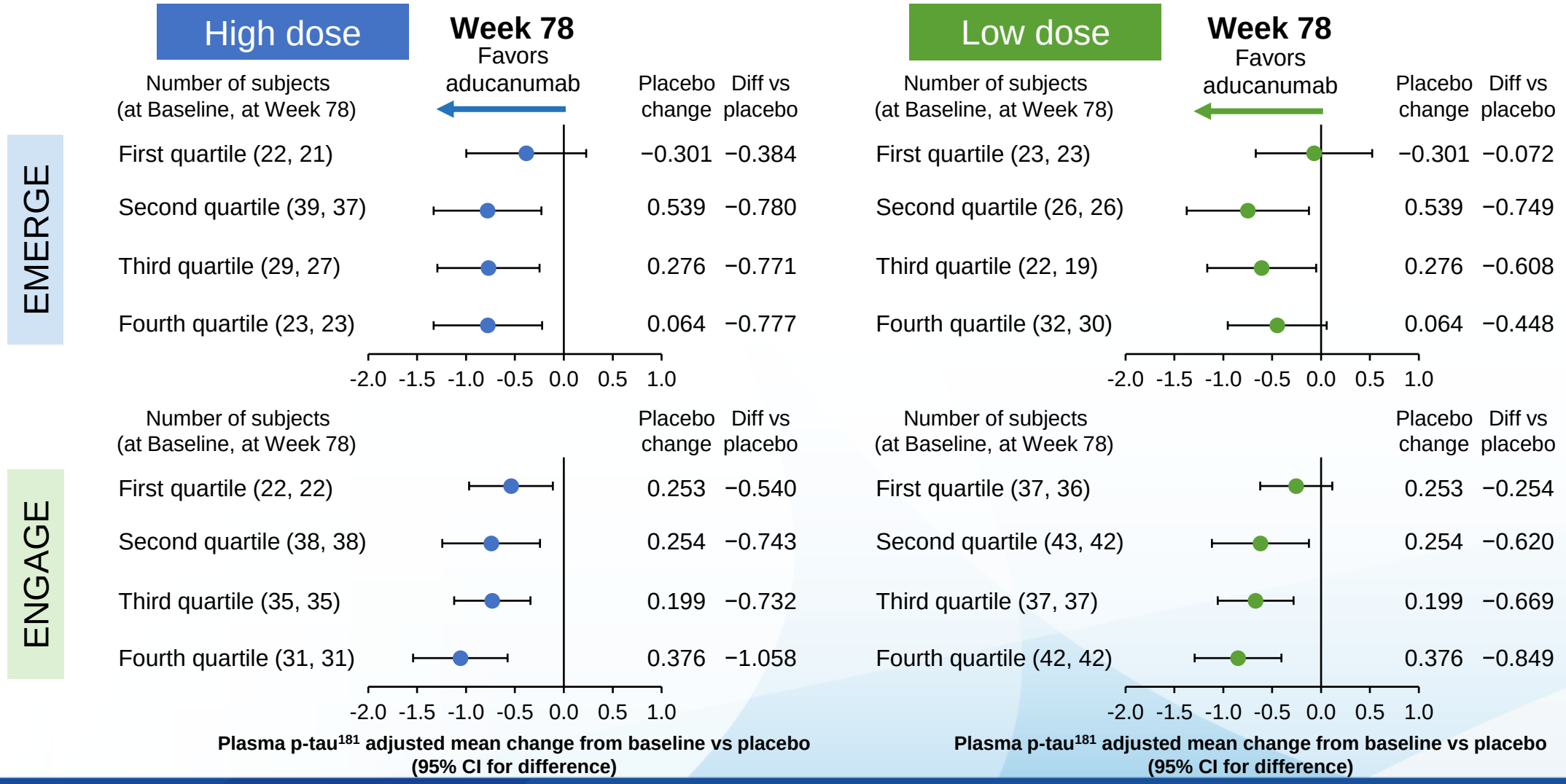
AD, Alzheimer's disease; CI, confidence interval; p-tau, phosphorylated tau.

Reduction in plasma p-tau^{181} levels favored aducanumab vs placebo in prespecified subgroups: baseline plasma p-tau^{181} levels



CI, confidence interval; p-tau, phosphorylated tau.

Reduction in plasma p-tau^{181} levels favored aducanumab vs placebo in prespecified subgroups: baseline amyloid PET SUVR



CI, confidence interval; PET, positron emission tomography; p-tau, phosphorylated tau; SUVR, standardized uptake value ratio.

Summary

- Evidence from a large data set demonstrated that aducanumab produced a significant dose- and time-dependent reduction in plasma p-tau^{181} levels in both EMERGE and ENGAGE
- Greater reduction in plasma p-tau^{181} levels was associated with lowering of amyloid PET SUVR and with less clinical decline across all 4 clinical measures in both studies
- Subgroup analysis revealed a consistent reduction in plasma p-tau^{181} levels in participants treated with aducanumab across all subgroups investigated, indicating a broad and consistent treatment effect across patients, regardless of baseline characteristics

PET, positron emission tomography; p-tau, phosphorylated tau; SUVR, standardized uptake value ratio.

Acknowledgments

We thank the Alzheimer’s disease community, all the patients and their family members participating in the aducanumab studies, and the investigators and their staff conducting these studies