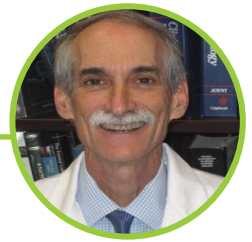
Late-breaking readout roundtable 8



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Discussant

[a] Stephen Salloway and Oskar Hansson are also authors on this presentation: *Dose- and time- dependent changes in plasma p-tau181 in patients treated with aducanumab in the ENGAGE and EMERGE trials*

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As always, the views expressed by all panelists are their own.

Disclosures

Authors/Panel Members

- SS receives research support for conduct of clinical trials from Lilly, Biogen, Genentech, Avid, Roche, Eisai and Novartis. He was a site PI for the PRIME, ENGAGE, Clarity and Trailblazer 1 trials. He is a co-chair of the investigator steering committee for the aducanumab phase 3 program and he is the Project Arm Leader for gantenerumab in the DIAN-TU study. He is a consultant to Lilly, Biogen, Roche, Genentech, Eisai, Bolden, Amylyx, NovoNordisk, Prothena, Ono and Alnylam. He owns no stocks or equity in any pharmaceutical company and has no patents or royalties
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Authors

- RR, TC, LN, YT, KKM, GD, PH, CCV, and SBH are employees and shareholders of Biogen

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Dose- and time- dependent changes in plasma p-tau^{181} in patients treated with aducanumab in the ENGAGE and EMERGE trials

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14th Clinical Trials on Alzheimer's Disease (CTAD) conference

November 9-12, 2021

Plasma p-tau is a novel, promising blood-based biomarker for Alzheimer's disease

Plasma p-tau levels are increased in AD

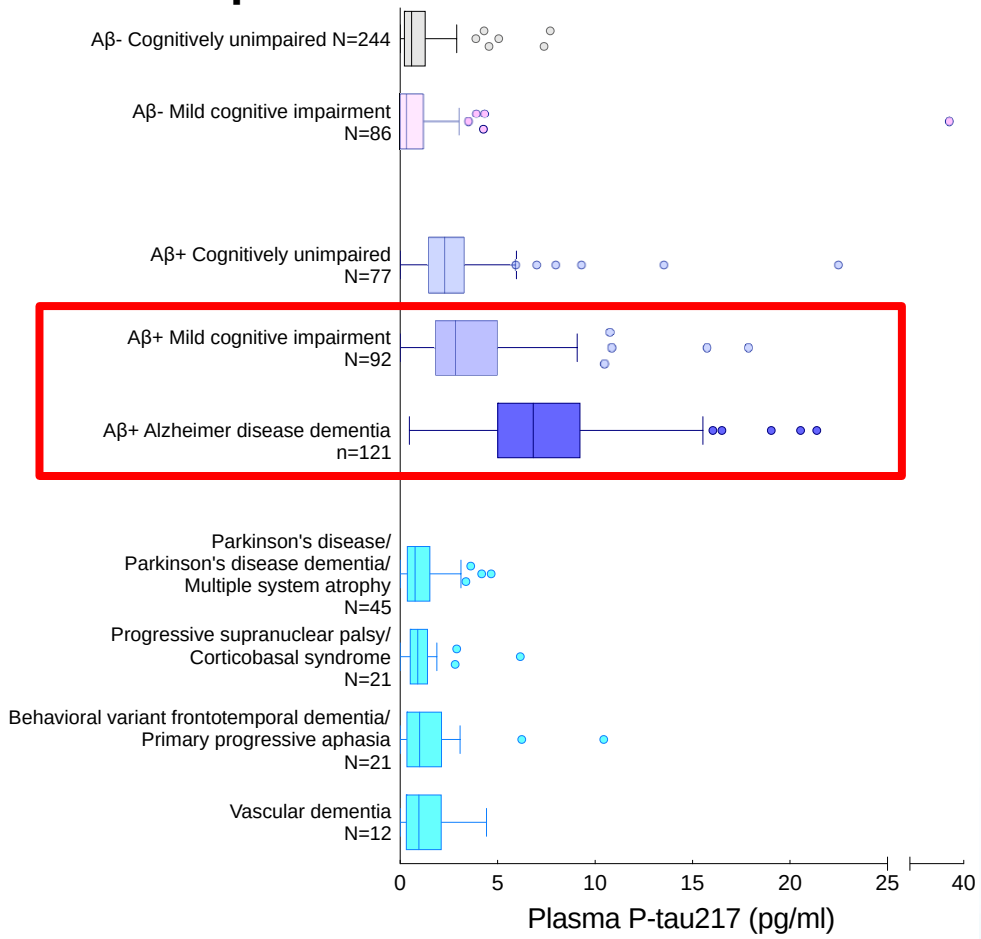


Figure adapted from Palmqvist S, et al. *JAMA*. 2020;324:772–781.[1]

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

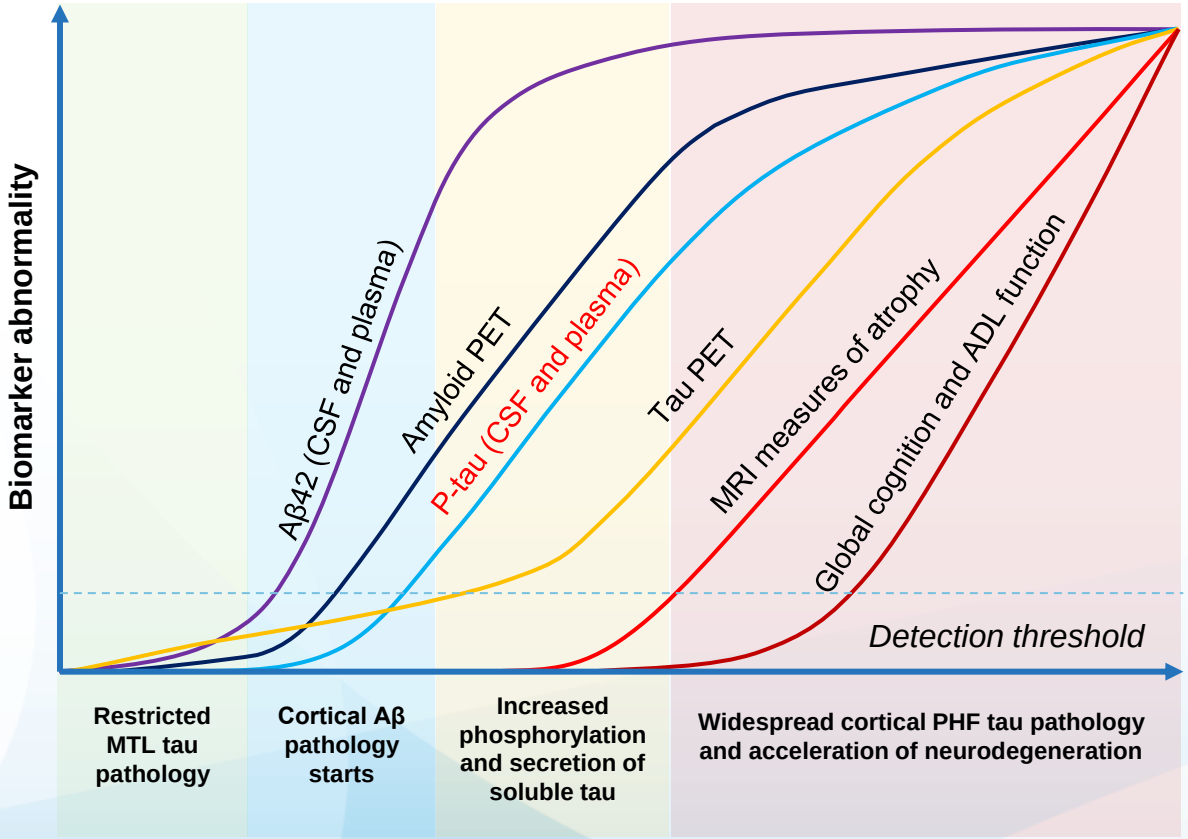


Figure adapted from Hansson O. *Nat Med*. 2021;27:954–963.[2]

Aβ, amyloid beta; ADL, activities of daily living; CSF, cerebrospinal fluid; FDG, fluorodeoxyglucose; MRI, magnetic resonance imaging; MTL, medial temporal lobe; p-tau, phosphorylated tau; PET, positron emission tomography; PHF, paired helical filaments; t-tau, total tau. 1. Palmqvist S, et al. *JAMA*. 2020;324:772–781; 2. Hansson O. *Nat Med*. 2021;27:954–963.

Soluble p-tau levels may mediate the relationship between amyloid aggregates and tau aggregates

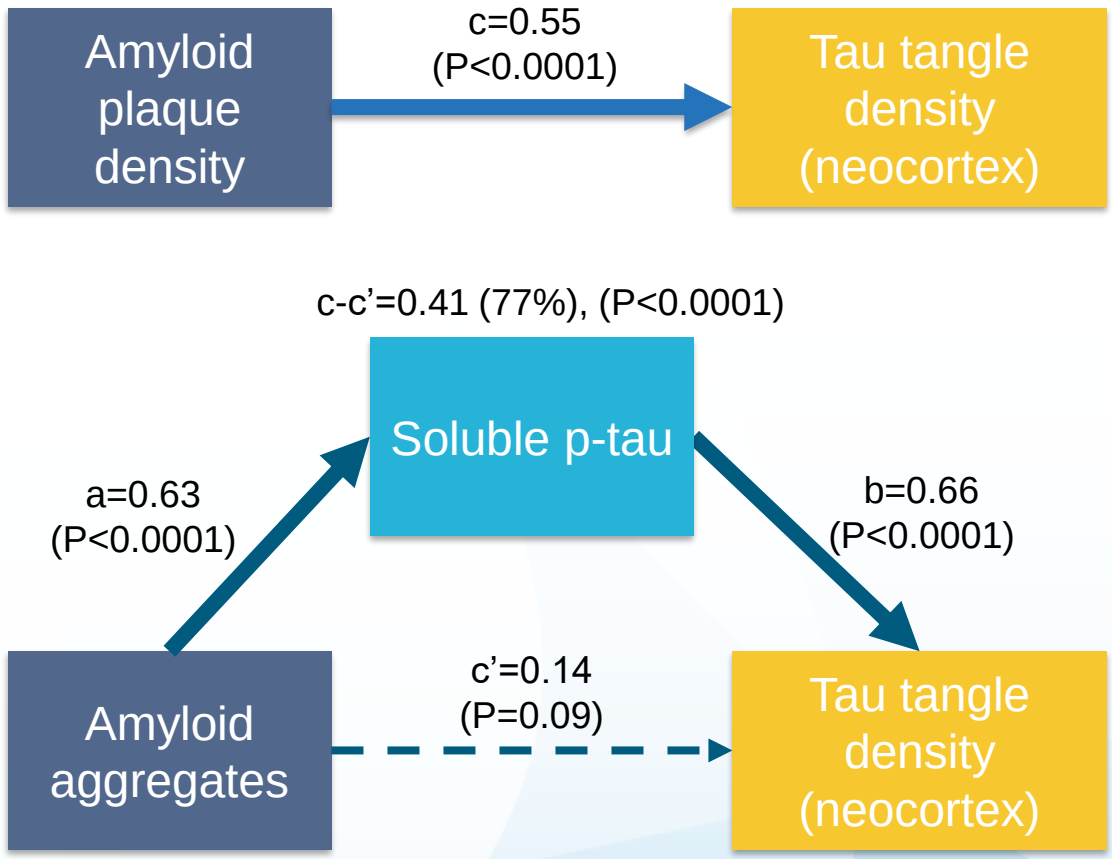
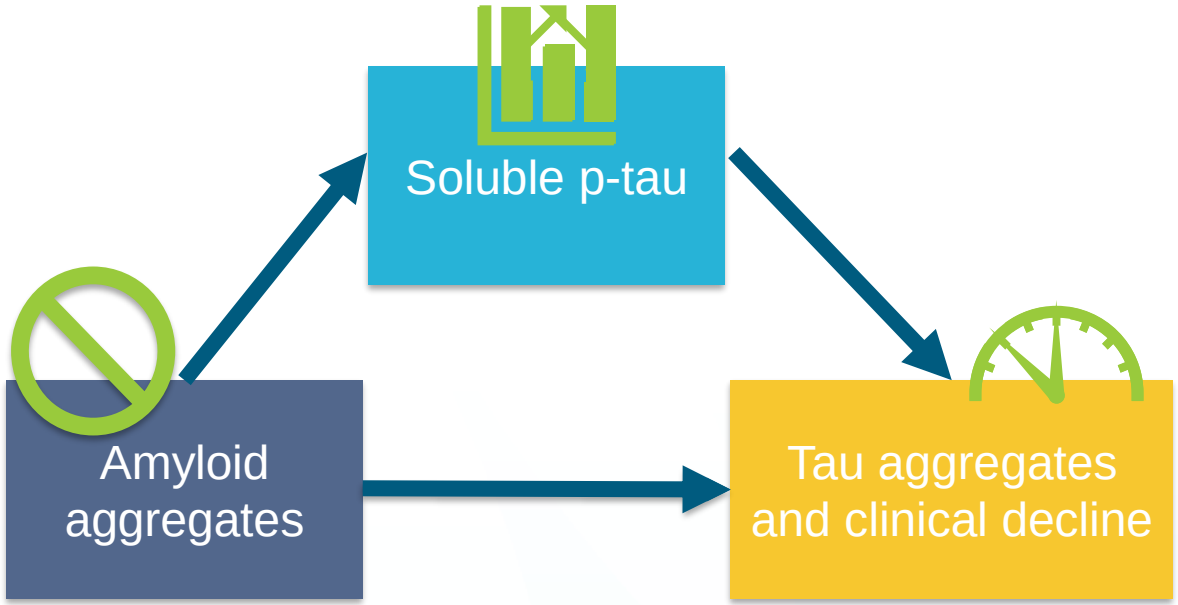


Figure adapted from Mattsson-Carlgren N, et al. *EMBO Mol Med*. 2021;13:e14022[1] and Mattsson-Carlgren N, et al. *Sci Adv*. 2020;6:eaaz2387.[2]

The strongest mediation was seen for total tangle density when removing tangles in the medial temporal lobe (77% mediation; the direct effect of Aβ plaques on tangles became non-significant)

Aβ, amyloid beta; p-tau, phosphorylated tau. 1. Mattsson-Carlgren N, et al. *EMBO Mol Med*. 2021;13:e14022; 2. Mattsson-Carlgren N, et al. *Sci Adv*. 2020;6:eaaz2387.

Soluble p-tau levels may mediate the relationship between amyloid aggregates and tau aggregates



- Amyloid-induced tau aggregation and spread (and consequent cognitive decline) might be driven by increases in soluble p-tau levels[1,2]
- Then, removing amyloid aggregates should result in reduced p-tau levels…
- …followed by slowing of accumulation of tau aggregates and clinical decline

P-tau, phosphorylated tau. 1. Mattsson-Carlgren N, et al. *EMBO Mol Med*. 2021;13:e14022; 2. Mattsson-Carlgren N, et al. *Sci Adv*. 2020;6:eaaz2387

Aducanumab Phase 3 studies (EMERGE and ENGAGE)

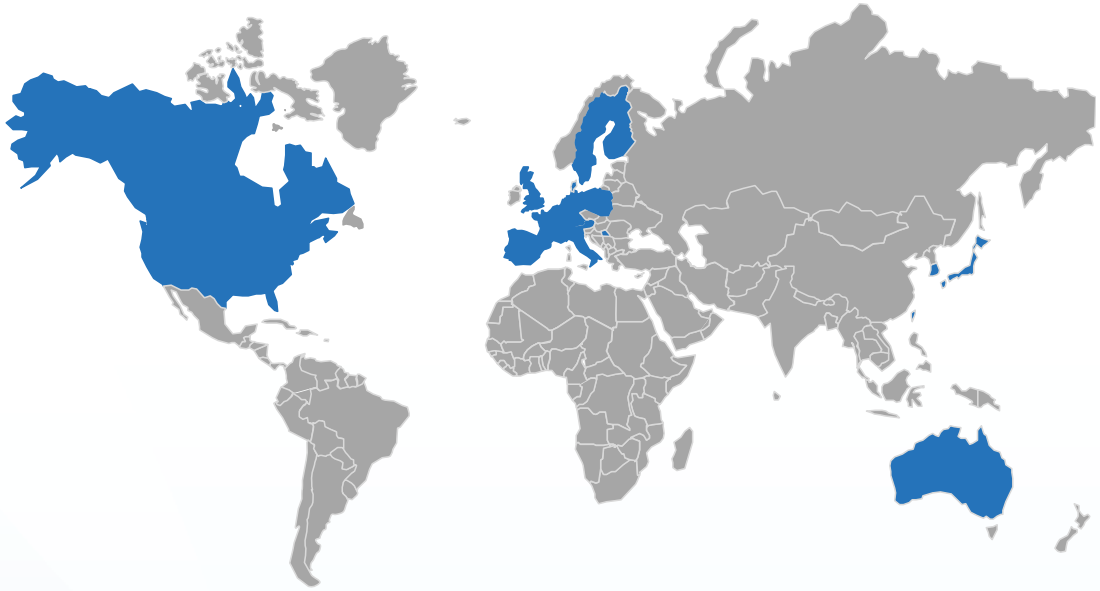
Study design: 18-month, randomised, double-blind, placebo-controlled, parallel-group studies designed to assess the efficacy, safety, pharmacokinetics, and pharmacodynamics of aducanumab

Study population: Early Alzheimer's disease (at MCI and mild Alzheimer's disease stages)

Primary endpoint: Change from baseline in CDR-SB score at 18 months

Secondary endpoints: MMSE, ADAS-Cog 13, ADCS-ADL-MCI

Biomarker endpoints: amyloid PET, tau PET, CSF disease-related biomarkers, plasma disease-related biomarkers

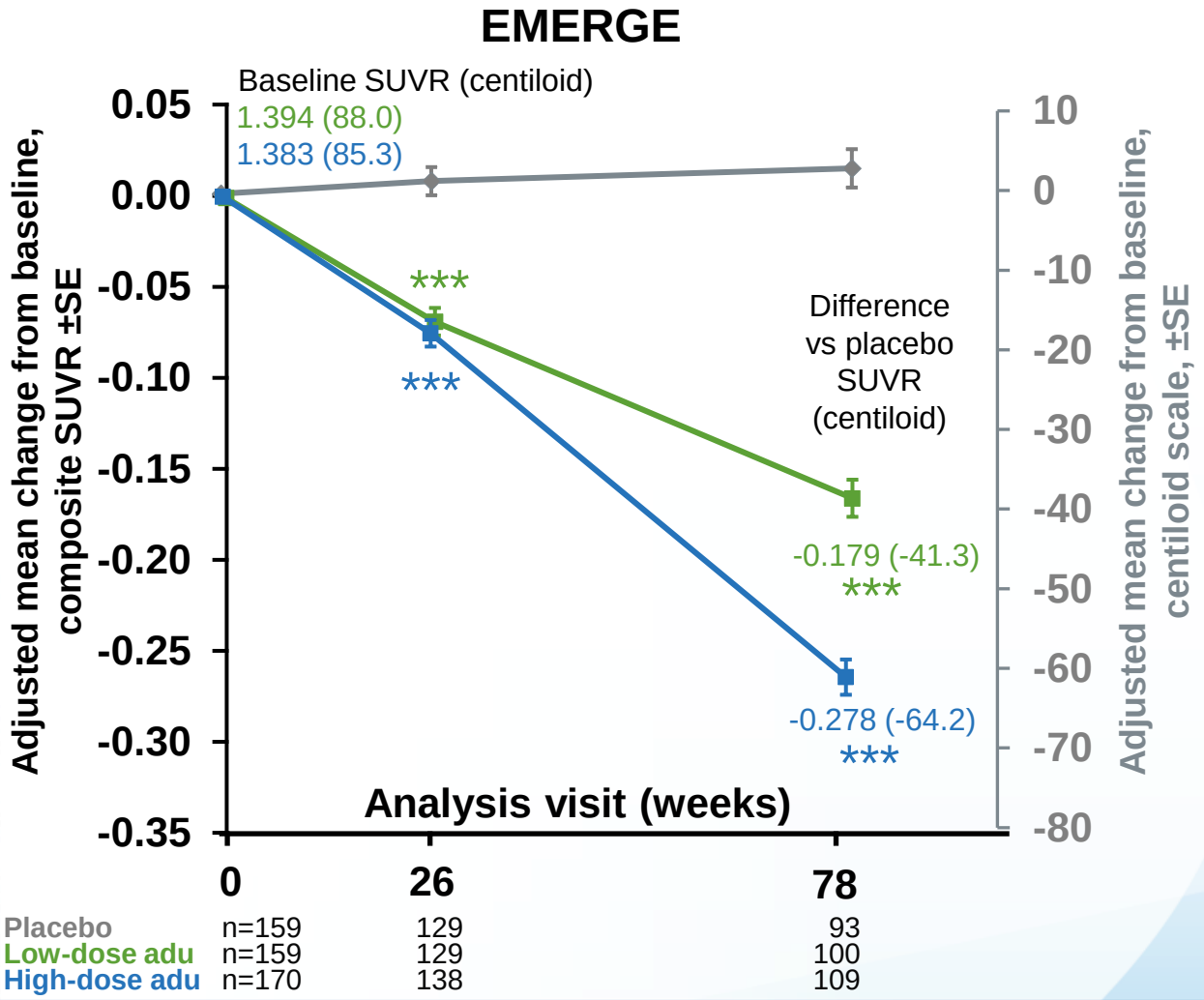


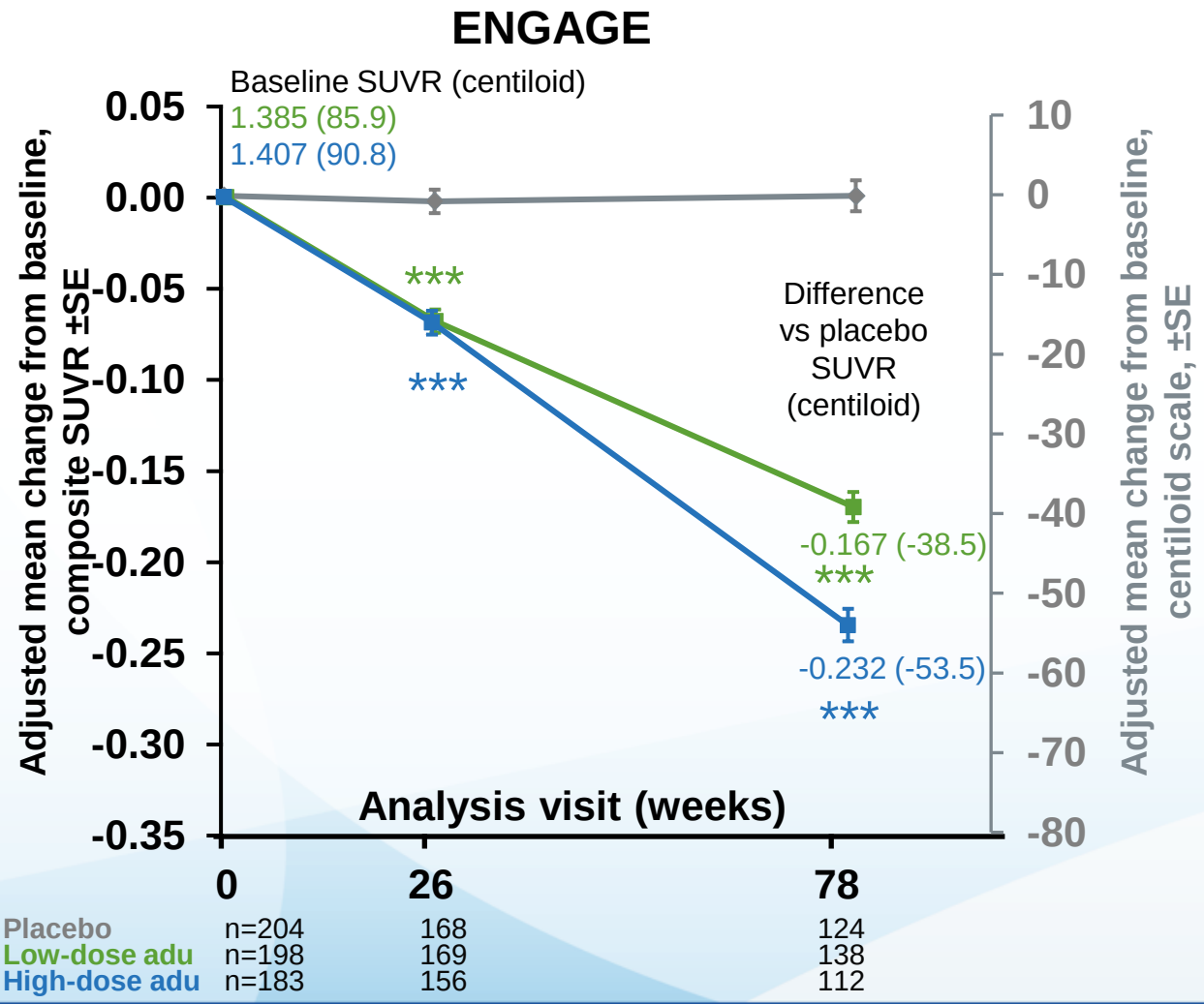
Global studies: 3285 patients at 348 sites in 20 countries

ADAS-Cog 13, Alzheimer's Disease Assessment Scale–Cognitive Subscale; 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.

Amyloid PET showed dose- and time-dependent reduction in β-amyloid pathology with aducanumab

Previously reported at ADPD 2021

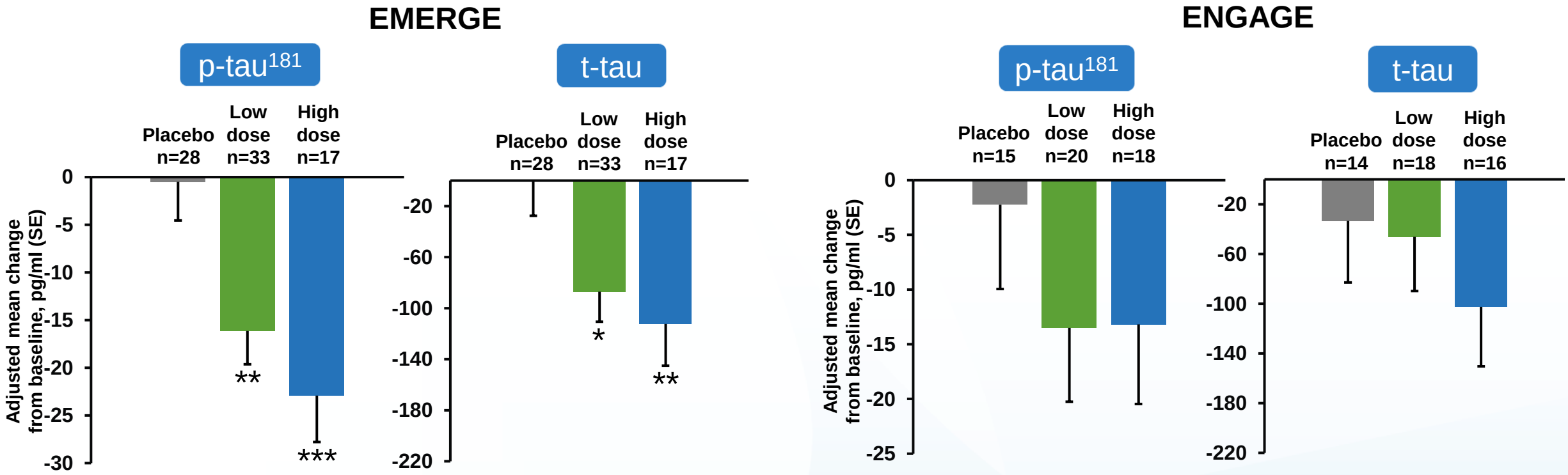




^{18}F-florbetapir amyloid PET analysis population. ***p<0.0001 compared with placebo (nominal). Values at each time point were based on an MMRM, with change from baseline in MMSE as the dependent variable and with fixed effects of treatment group, categorical visit, treatment-by-visit interaction, baseline SUVR, baseline SUVR by visit interaction, baseline MMSE, Alzheimer's disease symptomatic medication use at baseline, region, and laboratory ApoE ε4 status. adu, aducanumab; ApoE, apolipoprotein E; MMRM, mixed model for repeated measure; MMSE, Mini-Mental State Examination; PET, positron emission tomography; SE, standard error; SUVR, standardized uptake value ratio.

Aducanumab reduced CSF biomarkers of tau pathology and neurodegeneration at Week 78[a]

Previously reported at ADPD 2021



In EMERGE and ENGAGE, **aducanumab also reduced tau levels** in areas of the brain that have tau pathology at early stages of Alzheimer's disease (*tau PET pooled data)*

- Dose-dependent reduction in brain tau levels in the frontal, temporal and medial temporal composite brain regions

[a] Significant reduction for EMERGE and numerical for ENGAGE. CSF modified analysis population (patients with both baseline and post-baseline CSF assessments). *p<0.05, **p<0.01, ***p<0.001 compared with placebo (nominal). Values were based on an ANCOVA model at Week 78, fitted with change from baseline as the dependent variable, and with categorical treatment, baseline biomarker value, baseline age, and laboratory ApoE ε4 status (carrier and non-carrier) as the independent variables. Aβ, amyloid beta; ANCOVA, analysis of covariance; ApoE, apolipoprotein E; CSF, cerebrospinal fluid; p-tau, pg/ml, picograms per milliliter; phosphorylated tau; SE, standard error; t-tau, total tau.

Effect of aducanumab treatment on plasma p-tau^{181}

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 subjects were analyzed using the Quanterix Simoa p-tau^{181}Advantage V2 kit at Frontage Laboratories' (Exton, PA) CLIA laboratory
- The inter-assay CV was 6.49–8.15% and the intra-assay CV was 8.30–9.21%

	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.

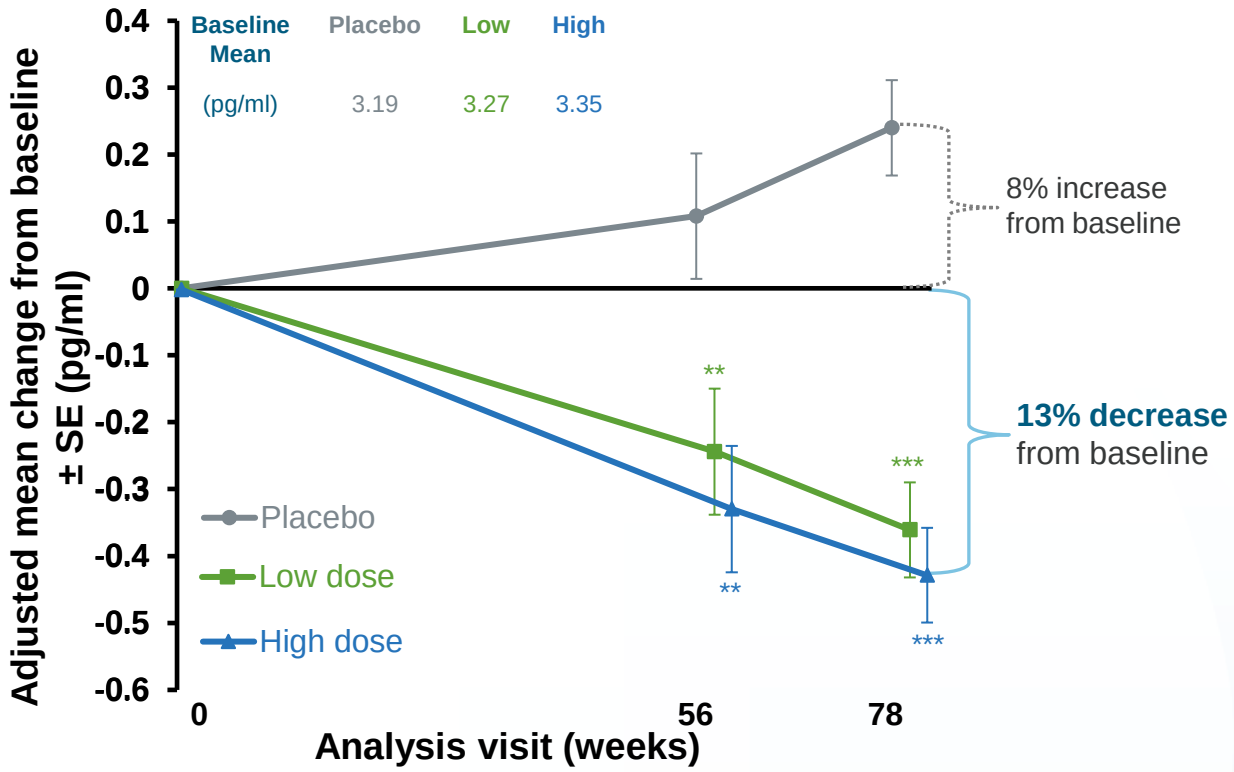
Baseline demographics and characteristics of Alzheimer's disease were similar across groups in the plasma p-tau^{181} analysis population

	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 in years, mean ± SD	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 (%)						
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 years, mean ± SD	14.7 ± 3.49	14.7 ± 3.38	14.7 ± 3.60	15.0 ± 3.56	14.7 ± 3.67	14.9 ± 3.75
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 (%)						
Carriers	199 (69.3)	197 (67.2)	187 (64.5)	230 (69.1)	231 (69.8)	195 (69.4)
Non-carriers	88 (30.7)	96 (32.8)	103 (35.5)	102 (30.6)	100 (30.2)	86 (30.6)
Clinical stage, n (%)						
MCI due to Alzheimer's disease	246 (85.7)	254 (86.7)	247 (85.2)	281 (84.4)	280 (84.6)	231 (82.2)
Mild Alzheimer's disease dementia	41 (14.3)	39 (13.3)	43 (14.8)	52 (15.6)	51 (15.4)	50 (17.8)

*Others not listed: American Indian or Alaska native, Native Hawaiian or other Pacific Islander, Not reported due to confidentiality regulations, or Unknown. ApoE, apolipoprotein E; MCI, mild cognitive impairment; p-tau, phosphorylated tau; SD, standard deviation.

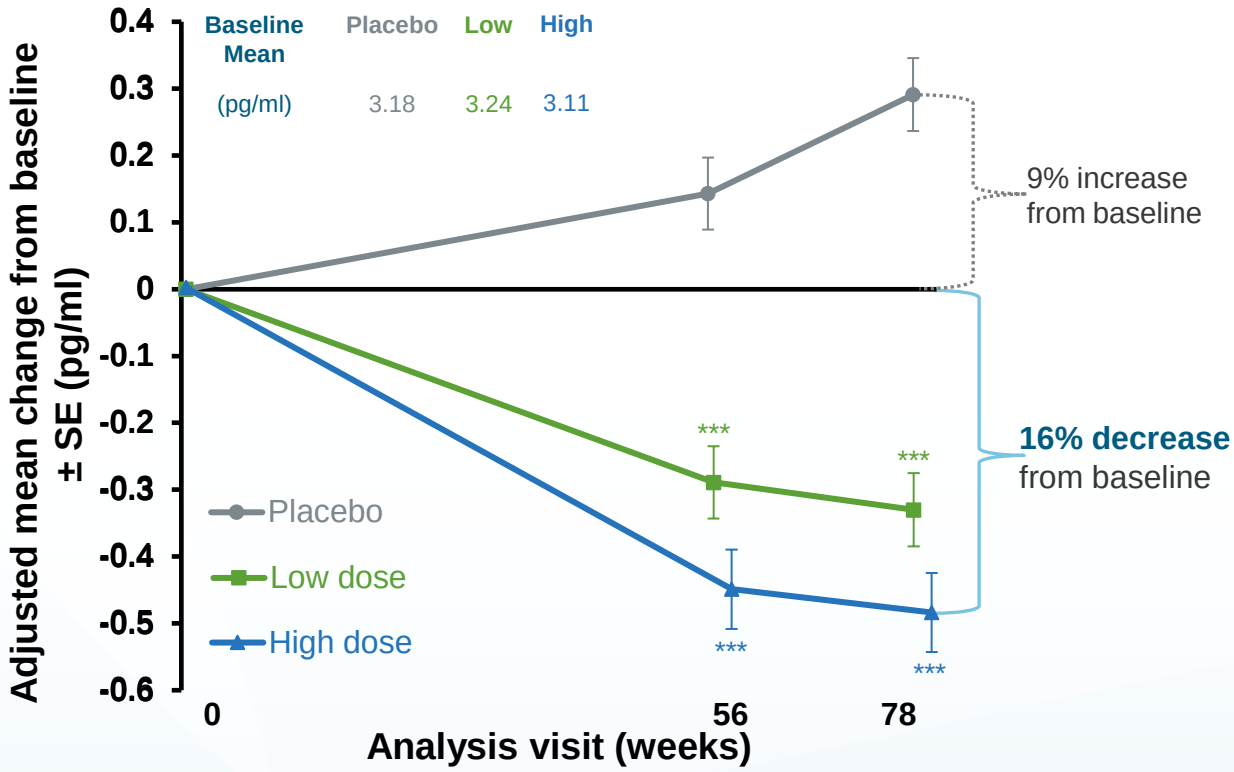
Aducanumab significantly lowers plasma p-tau^{181}

EMERGE



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

ENGAGE

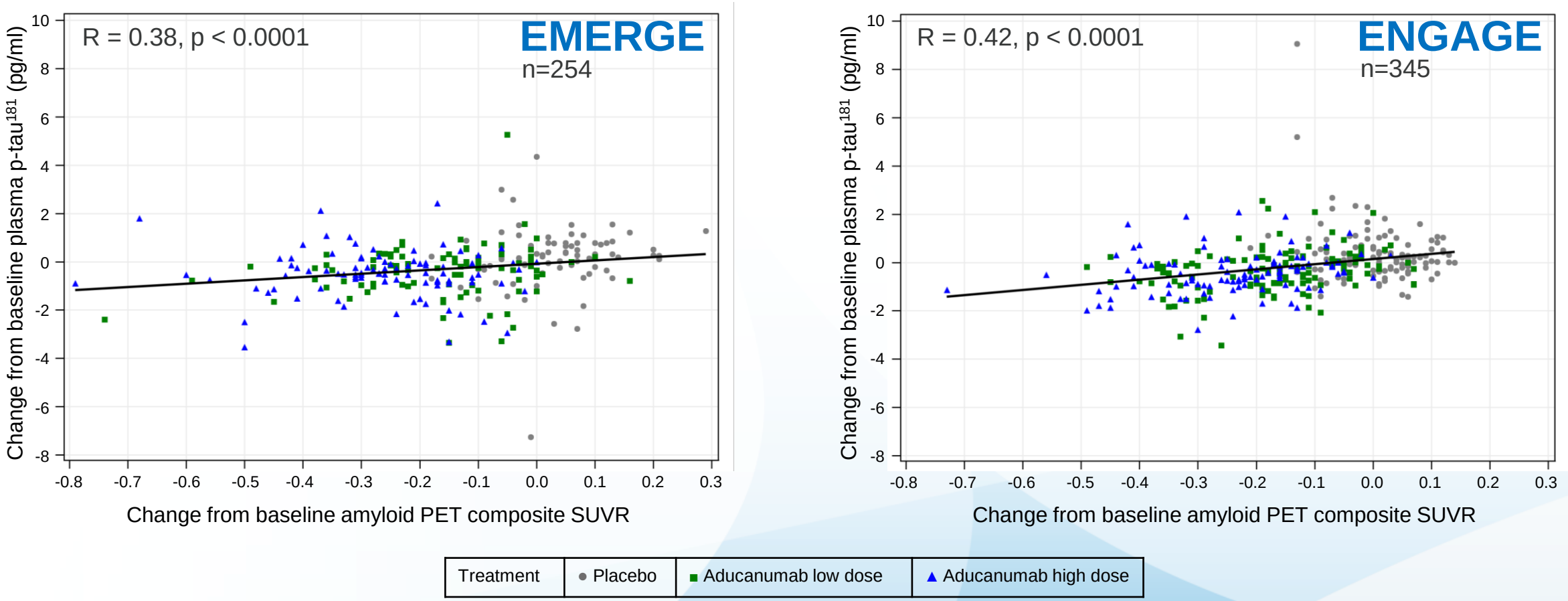


Placebo	333	301	325
Low dose	331	299	322
High dose	281	242	274

*p<0.05, **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.

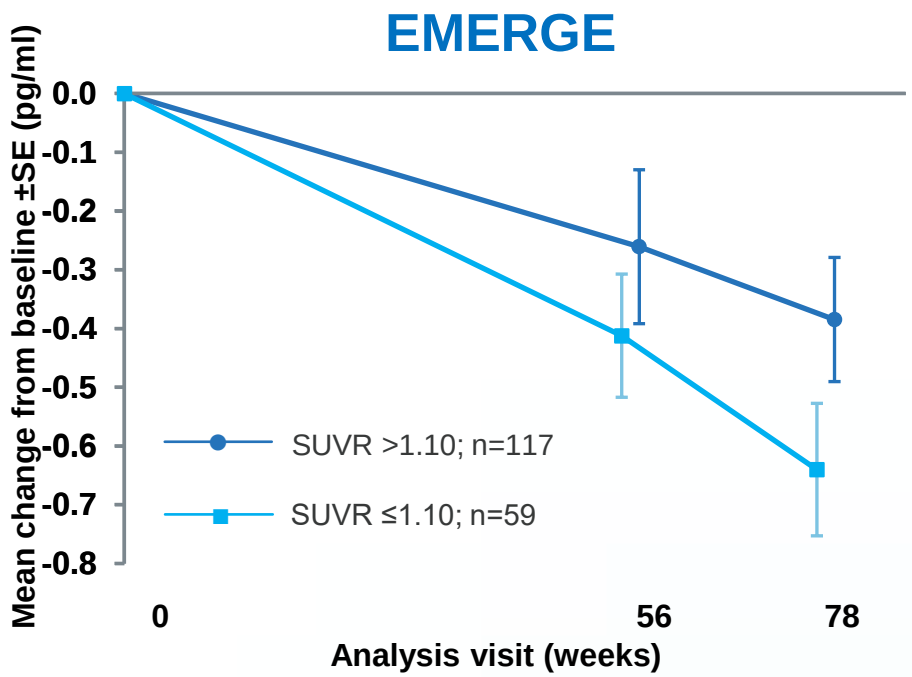
Change in plasma p-tau^{181} is correlated with change in amyloid PET SUVR at Week 78

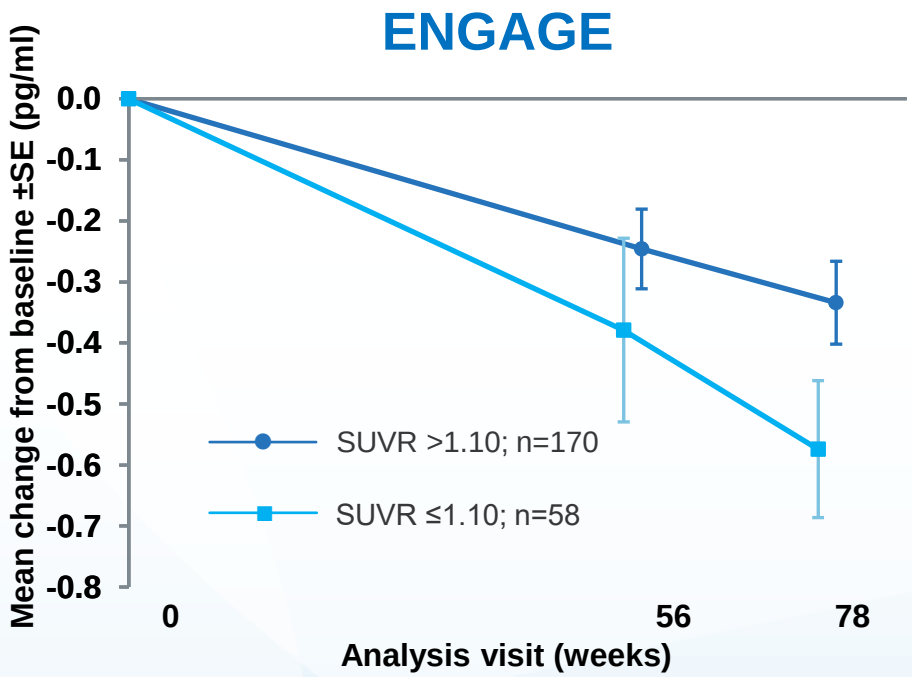
Scatterplots of change from baseline plasma p-tau^{181} vs change from baseline florbetapir amyloid PET composite SUVR (reference region = cerebellum) at Week 78



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.

Reduction in plasma p-tau^{181} was greater in aducanumab-treated subjects who had an amyloid PET SUVR ≤1.10 at Week 78





Assessed in pooled low and high dose aducanumab-treated groups. A SUVR of 1.10 is a threshold reported to discriminate between positive and negative florbetapir amyloid PET.[1] PET, positron emission tomography; pg/ml, picograms per milliliter; p-tau, phosphorylated tau; SUVR, standardized uptake value ratio. 1. Joshi AD, et al. *J Nucl Med*. 2015;56:1736–1741.

Greater reduction in plasma p-tau^{181} is associated with less clinical decline across all four clinical measures in both studies

Association between change in p-tau and efficacy at Week 78		Expected 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-Cog13	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; 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.

Summary

- Evidence from a large dataset (~7,000 plasma samples from 1815 patients with early Alzheimer's disease) demonstrated that aducanumab produces a significant dose- and time-dependent reduction in plasma p-tau^{181} consistently in both EMERGE and ENGAGE
- The treatment effect of aducanumab on plasma p-tau^{181} was associated with lowering of amyloid PET SUVR and reduced cognitive and functional decline
  - This is consistent with the hypothesized relationship among the underlying pathologies of Alzheimer's disease
- These findings demonstrated that modification of biomarkers fundamental to the underlying disease pathology was associated with statistically significant slowing of clinical decline as measured by CDR-SB, MMSE, ADAS-Cog13, and ADCS-ADL-MCI

ADAS-Cog 13, Alzheimer's Disease Assessment Scale–Cognitive Subscale; 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; 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, as well as the investigators and their staff conducting these studies