Evaluation of aducanumab efficacy in early Alzheimer's disease

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AD/PD 2021, Virtual Conference

March 9-14, 2021

Disclosures

- SBH, CCV, TC, PH, CM, KKM, LN, RR, SW, LY, and YT are employees of Biogen and may be stockholders
- SS was a site investigator and co-chair of the Investigator Steering Committee for the ENGAGE study and is a consultant to Biogen. He also receives research support and is a consultant to Eisai, Novartis, Genentech, Roche, Avid, and Lilly
- PSA was Chair of the Steering Committee, has received research support from Lilly, Janssen, Eisai, the Alzheimer Association, NIH and FNIH, and has consulted for Merck, Roche and ImmunoBrain Checkpoint
- FB was supported by NIHR Biomedical Research Centre at UCLH. He receives personal fees for consultancy from Bayer, Biogen, Roche, IXICO Ltd, Novartis and Combinostics
- SC was an ENGAGE trial site investigator and an Aducanumab Steering Committee member. She is a consultant to Biogen, Cogstate, ProMIS Neuroscience, and RetiSpec and receives research support (paid to institution) from AgeneBio, Alector, Anavex, Biogen, CCHI, Eisai, Genentech, Green Valley, Eli Lilly, RetiSpec, Roche, and Vielight
- 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
- TI is a consultant to Eisai and Roche
- CJM was an ENGAGE trial site investigator and an Aducanumab Steering Committee member. She is supported by NIHR Biomedical Research Centre at UCLH and has acted as a consultant to Biogen, Roche, and IONIS
- BV has no conflicts of interest to disclose

Forward-looking statements

- This presentation contains forward-looking statements, including statements made pursuant to the safe harbor provisions of the Private Securities Litigation Reform Act of 1995, relating to additional results from the Phase 3 clinical studies of aducanumab; the potential clinical effects of aducanumab; the potential benefits, safety, and efficacy of aducanumab; potential regulatory discussions, submissions, and approvals and the timing thereof; clinical development programs, clinical trials, data readouts, and presentations related to aducanumab; the enrollment of any future clinical studies of aducanumab; the treatment of Alzheimer's disease; the potential of Biogen's commercial business and pipeline programs, including aducanumab; the anticipated benefits and potential of Biogen's collaboration arrangements with Eisai Co, Ltd; and risks and uncertainties associated with drug development and commercialization. These forward-looking statements may be accompanied by such words as "aim," "anticipate," "believe," "could," "estimate," "expect," "forecast," "intend," "may," "plan," "potential," "possible," "will," "would," and other words and terms of similar meaning. Drug development and commercialization involve a high degree of risk, and only a small number of research and development programs result in commercialization of a product. Results in early-stage clinical trials may not be indicative of full results or results from later-stage or larger-scale clinical trials and do not ensure regulatory approval. You should not place undue reliance on these statements or the scientific data presented.

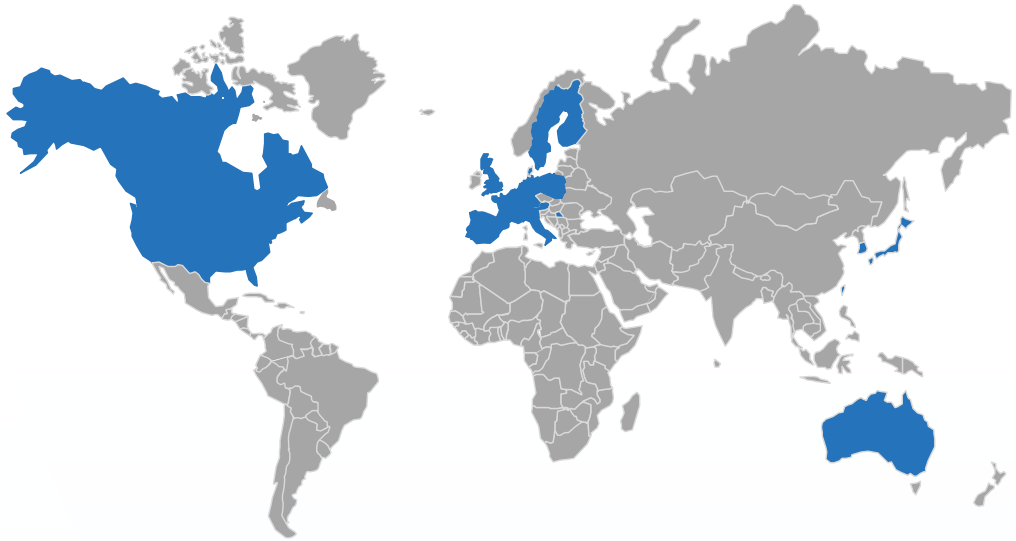
- These statements involve risks and uncertainties that could cause actual results to differ materially from those reflected in such statements, including actual timing and content of submissions to and decisions made by the regulatory authorities regarding aducanumab; regulatory submissions may take longer or be more difficult to complete than expected; regulatory authorities may require additional information or further studies, or may fail or refuse to approve or may delay approval of Biogen's drug candidates, including aducanumab; actual timing and enrollment of future studies of aducanumab; the occurrence of adverse safety events and/or unexpected concerns that may arise from additional data or analysis; risks of unexpected costs or delays; the risks of other unexpected hurdles; uncertainty of success in the development and potential commercialization of aducanumab; failure to protect and enforce Biogen's data, intellectual property, and other proprietary rights and uncertainties relating to intellectual property claims and challenges; risks relating to the potential launch of aducanumab, including preparedness of healthcare providers to treat patients, the ability to obtain and maintain adequate reimbursement for aducanumab, and other unexpected difficulties or hurdles; product liability claims; third-party collaboration risks; and the other risks and uncertainties that are described in the Risk Factors section of our most recent annual or quarterly report and in other reports we have filed with the U.S. Securities and Exchange Commission. These statements are based on our current beliefs and expectations and speak only as of the date of this presentation. We do not undertake any obligation to publicly update any forward-looking statements, whether as a result of new information, future developments, or otherwise.

Statement on aducanumab

- Aducanumab is an investigational drug whose efficacy and safety have not yet been established. It is not approved for use in any country.
- Biogen licensed the worldwide rights to aducanumab from Neurimmune Holding AG in 2007 and is responsible for its development and commercialization.
- As of October 22, 2017, Biogen and Eisai are collaborating on the development and commercialization of aducanumab globally.

Aducanumab Phase 3 studies EMERGE and ENGAGE

Studies	Two 18-month, randomized, double-blind, placebo-controlled, Phase 3 studies
Geography/ sample size	3285 patients at 348 sites in 20 countries
Population	▪ Early Alzheimer's disease (MCI due to Alzheimer's disease + mild Alzheimer's disease dementia) • MMSE 24-30, CDR-GS 0.5, RBANS DMI score ≤ 85 • Confirmed amyloid pathology
Doses	▪ Two dosing regimens (low and high dose) and placebo; randomized 1:1:1
Primary endpoint	▪ Change from baseline in CDR-SB score at 18 months
Other endpoints	▪ Secondary: MMSE, ADAS-Cog 13, ADCS-ADL-MCI ▪ Tertiary (efficacy): NPI-10 ▪ Sub-studies: amyloid PET, tau PET, CSF disease-related biomarkers



Countries with active sites included:
Australia, Austria, Belgium, Canada, Denmark, Finland, France, Germany, Italy, Japan, the Netherlands, Poland, Portugal, South Korea, Spain, Sweden, Switzerland, Taiwan, United Kingdom, United States

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-GS, Clinical Dementia Rating Scale–Global; CDR-SB, Clinical Dementia Rating–Sum of Boxes; CSF, cerebrospinal fluid; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; NPI-10, Neuropsychiatric Inventory (10-item); PET, positron-emission tomography; RBANS DMI, Repeatable Battery for Assessment of Neuropsychological Status–Delayed Memory Index.

ClinicalTrials.gov: https://clinicaltrials.gov/ct2/show/NCT02477800. Accessed November 2019; ClinicalTrials.gov: https://clinicaltrials.gov/ct2/show/NCT02484547. Accessed November 2019.

Background

- Two randomized clinical trials, EMERGE and ENGAGE were conducted in 3285 patients with early Alzheimer's disease
- A prespecified interim analysis for futility was conducted, per protocol, after approximately 50% of the participants had the opportunity to complete Week 78
- EMERGE and ENGAGE were halted in March 2019 based on the results of the futility analysis
- Based on a larger dataset after the trials were terminated, it was determined that the assumptions in the futility analysis were not valid
- After collection of data at safety follow-up visits, databases were locked and analyzed per the prespecified analysis plan; data were censored following the futility announcement
- Aducanumab is currently under review by the FDA (US), EMA (EU), and PDMA (Japan)

EMA, European Medicines Agency; EU, European Union; FDA, Food and Drug Administration; PDMA, Product Development and Management Association; US, United States.

Baseline demographics

	EMERGE			ENGAGE		
	Placebo (n=548)	**Low dose** (n=543)	**High dose** (n=547)	**Placebo** (n=545)	**Low dose** (n=547)	**High dose** (n=555)
Age in years, mean ± SD	70.8±7.4	70.6±7.4	70.6±7.5	69.8±7.7	70.4±7.0	70.0±7.7
Female, n (%)	290 (53)	269 (50)	284 (52)	287 (53)	284 (52)	292 (53)
Race, n (%)						
Asian	47 (9)	39 (7)	42 (8)	55 (10)	55 (10)	65 (12)
White	431 (79)	432 (80)	422 (77)	413 (76)	412 (75)	413 (74)
Education years, mean ± SD	14.5±3.7	14.5±3.6	14.5±3.6	14.7±3.7	14.6±3.8	14.6±3.7
Alzheimer's disease medications used, n (%)	282 (51)	281 (52)	285 (52)	299 (55)	317 (58)	313 (56)
ApoE ε4, n (%)						
Carriers	368 (67)	362 (67)	365 (67)	376 (69)	391 (71)	378 (68)
Non-carriers	178 (32)	178 (33)	181 (33)	167 (31)	156 (29)	176 (32)
Clinical stage, n (%)						
MCI due to Alzheimer's disease	446 (81)	452 (83)	438 (80)	443 (81)	440 (80)	442 (80)
Mild Alzheimer's disease dementia	102 (19)	91 (17)	109 (20)	102 (19)	107 (20)	113 (20)

ITT population.
ApoE, apolipoprotein E; ITT, intent to treat; MCI, mild cognitive impairment; SD, standard deviation.

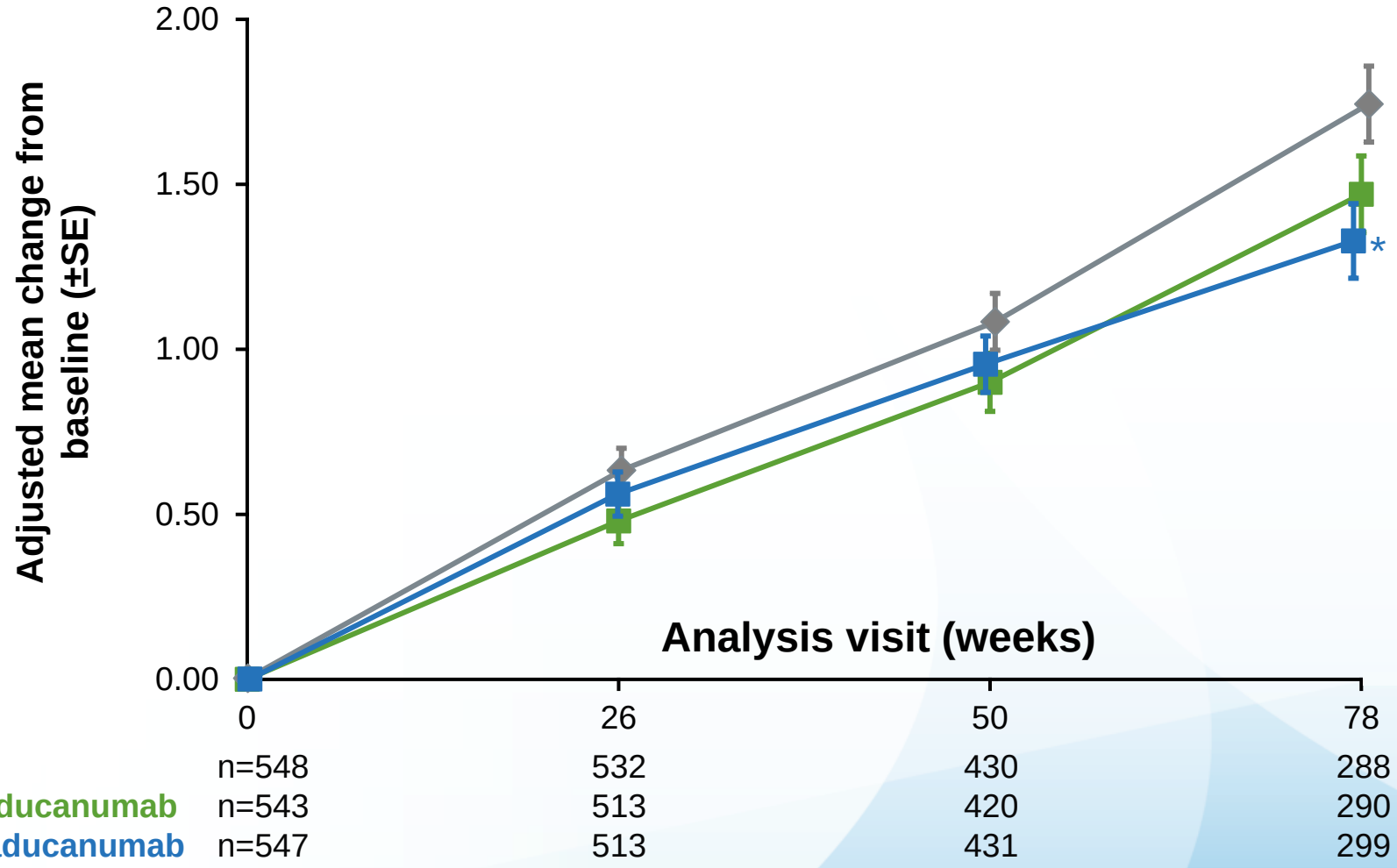
Baseline disease characteristics

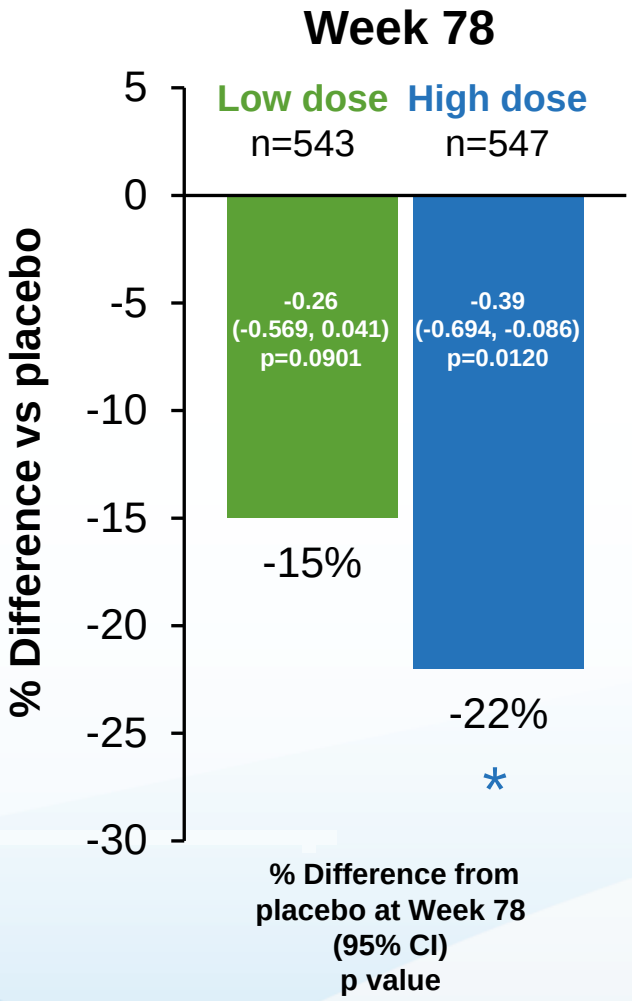
	EMERGE			ENGAGE		
	Placebo (n=548)	**Low dose** (n=543)	**High dose** (n=547)	**Placebo** (n=545)	**Low dose** (n=547)	**High dose** (n=555)
RBANS delayed memory score, mean ± SD	60.5±14.2	60.0±14.0	60.7±14.2	60.0±13.6	59.5±14.2	60.6±14.1
MMSE score, mean ± SD	26.4±1.8	26.3±1.7	26.3±1.7	26.4±1.7	26.4±1.8	26.4±1.8
CDR global score, n (%)						
0.5	545 (99)	543 (100)	546 (100)	544 (100)	546 (100)	554 (100)
1	3 (1)	0	1 (0)	1 (0)	1 (0)	0
CDR-SB score, mean ± SD	2.47±1.00	2.46±1.01	2.51±1.05	2.40±1.01	2.43±1.01	2.40±1.01
ADAS-Cog 13 score, mean ± SD	21.87±6.73	22.49±6.76	22.25±7.07	22.48±6.56	22.52±6.30	22.40±6.54
ADCS-ADL-MCI score, mean ± SD	42.6±5.7	42.8±5.5	42.5±5.8	43.0±5.6	42.9±5.7	42.9±5.7
PET substudy population	n=159	n=159	n=170	n=204	n=198	n=183
Amyloid PET SUVR, mean composite ± SD	1.37±0.17	1.39±0.18	1.38±0.18	1.38±0.20	1.39±0.19	1.41±0.18

ITT population.
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, Clinical Dementia Rating; CDR-SB, Clinical Dementia Rating–Sum of Boxes; ITT, intent to treat; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; RBANS, Repeatable Battery for Assessment of Neuropsychological Status; PET, positron-emission tomography; SD, standard deviation; SUVR, standardized uptake value ratio.

EMERGE: Longitudinal change from baseline in CDR-SB

The primary endpoint of change from baseline in CDR-SB at Week 78 was met

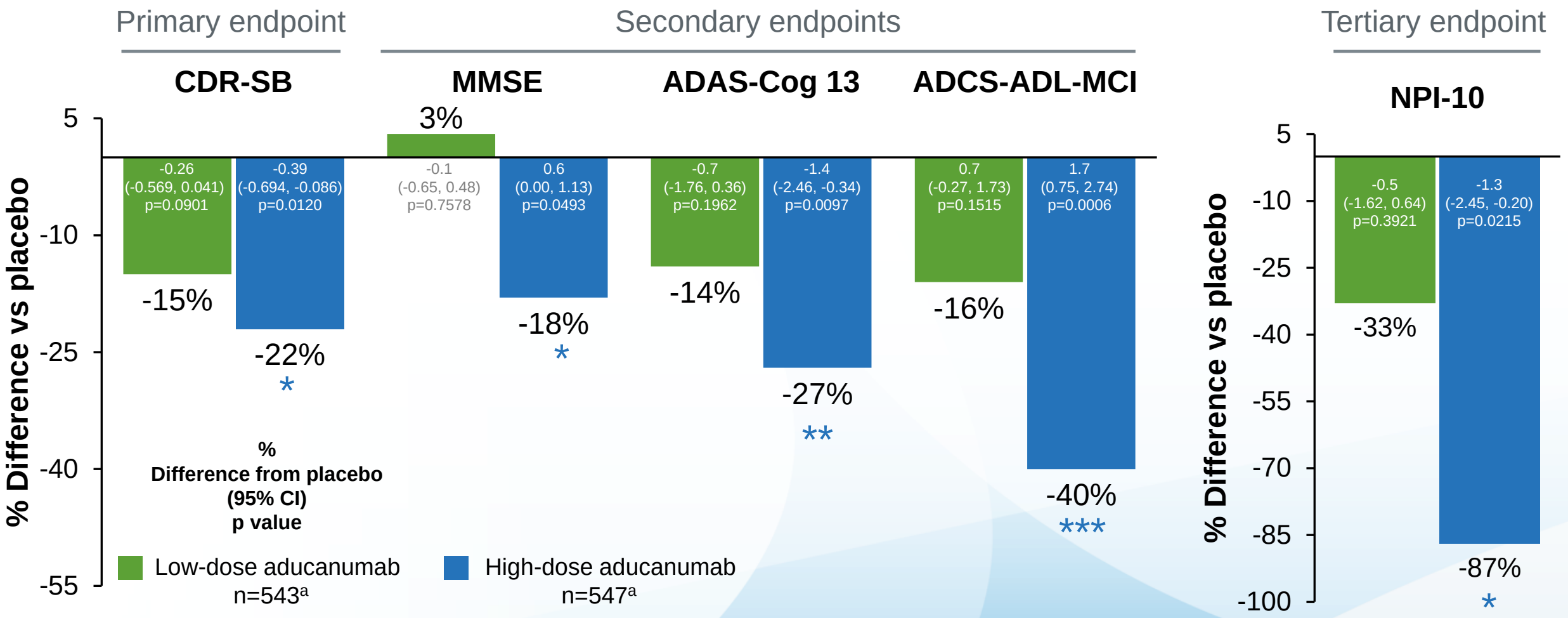




ITT population. *p <0.05 compared with placebo. Values at each time point were based on an MMRM model, with change from baseline in CDR-SB as the dependent variable and with fixed effects of treatment group, categorical visit, treatment-by-visit interaction, baseline CDR-SB, baseline CDR-SB by visit interaction, baseline MMSE, Alzheimer's disease symptomatic medication use at baseline, region, and laboratory ApoE ε4 status.
ApoE, apolipoprotein E; CDR-SB, Clinical Dementia Rating–Sum of Boxes; CI, confidence interval; ITT, intent to treat; MMRM, mixed model for repeated measure; MMSE, Mini Mental State Examination; SE, standard error.

EMERGE: Clinical endpoints at Week 78

High dose aducanumab met all clinical endpoints assessing cognition, function and behavior at Week 78



[a] n=numbers of randomized and dosed patients included in the analysis. *p <0.05, **p <0.01, and ***p <0.001 compared with placebo (nominal for NPI-10).
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; CI, confidence interval; MMSE, Mini-Mental State Examination; NPI-10, Neuropsychiatric Inventory (10-item).

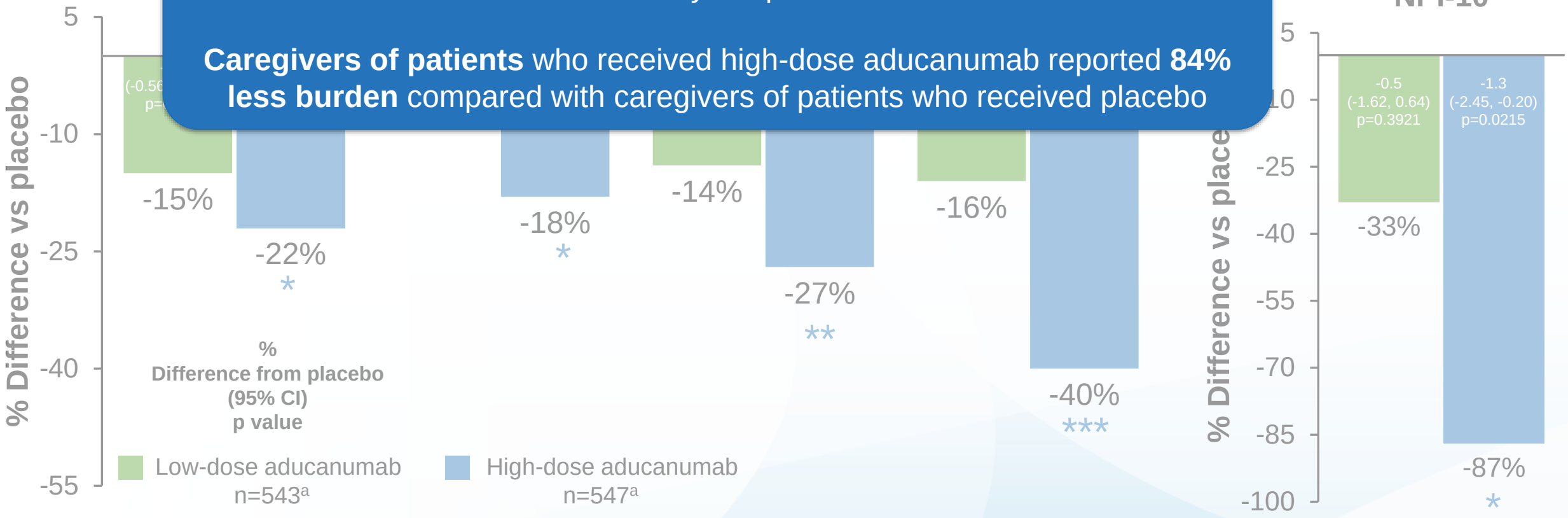
EMERGE: Clinical endpoints at Week 78

High dose aducanumab met all clinical endpoints assessing cognition, function and behavior at Week 78

Tertiary endpoint

Treatment effect was also observed on the NPI-10, an exploratory clinical efficacy endpoint

Caregivers of patients who received high-dose aducanumab reported **84% less burden** compared with caregivers of patients who received placebo



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Tertiary endpoint

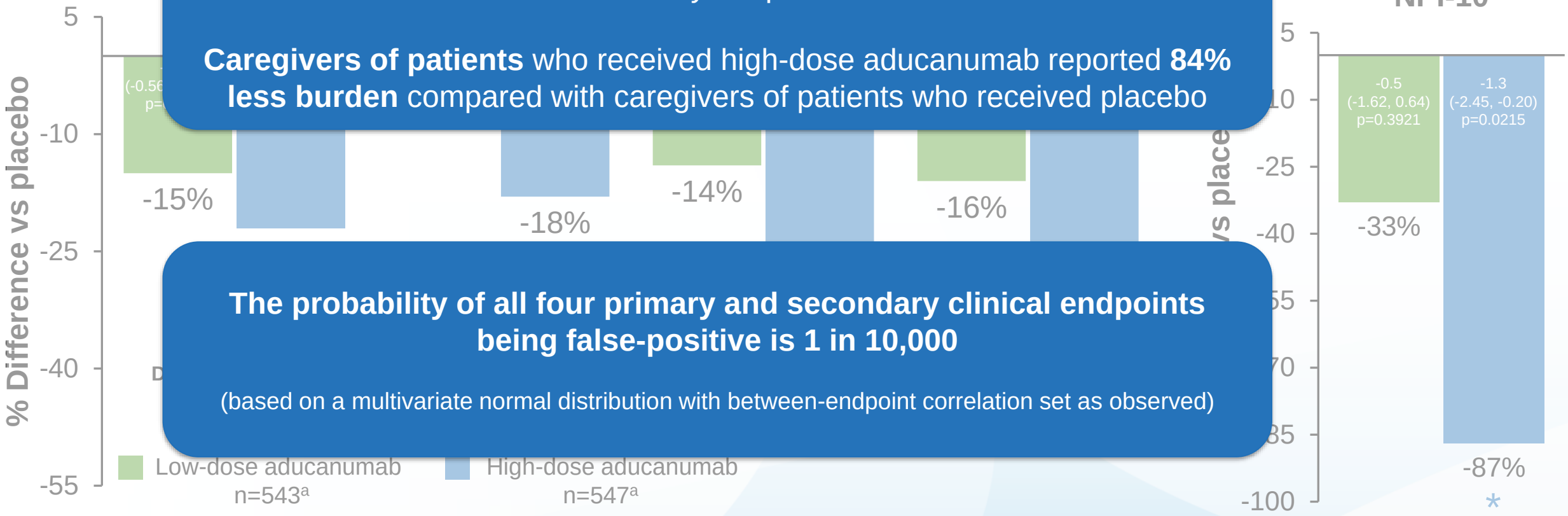
NPI-10

Treatment effect was also observed on the NPI-10, an exploratory clinical efficacy endpoint

Caregivers of patients who received high-dose aducanumab reported **84% less burden** compared with caregivers of patients who received placebo

The probability of all four primary and secondary clinical endpoints being false-positive is 1 in 10,000

(based on a multivariate normal distribution with between-endpoint correlation set as observed)



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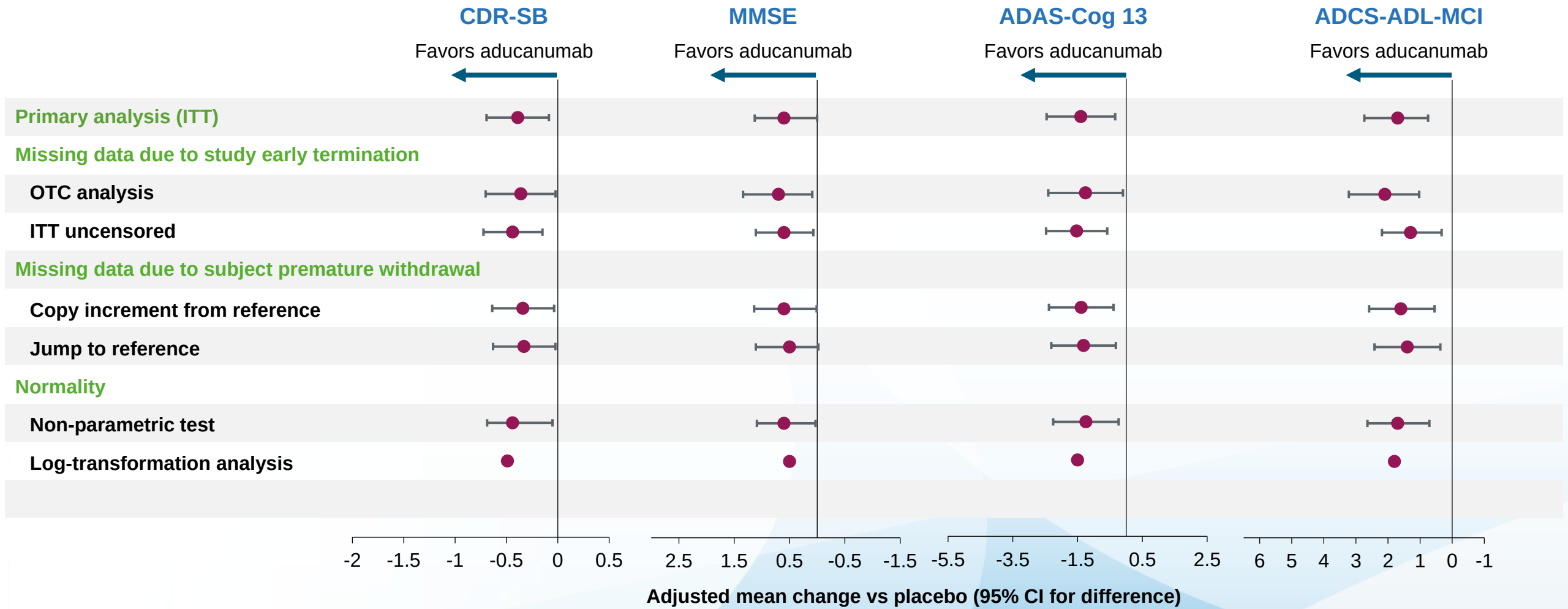
EMERGE: Sensitivity analyses assessed the robustness of treatment effect with high-dose aducanumab



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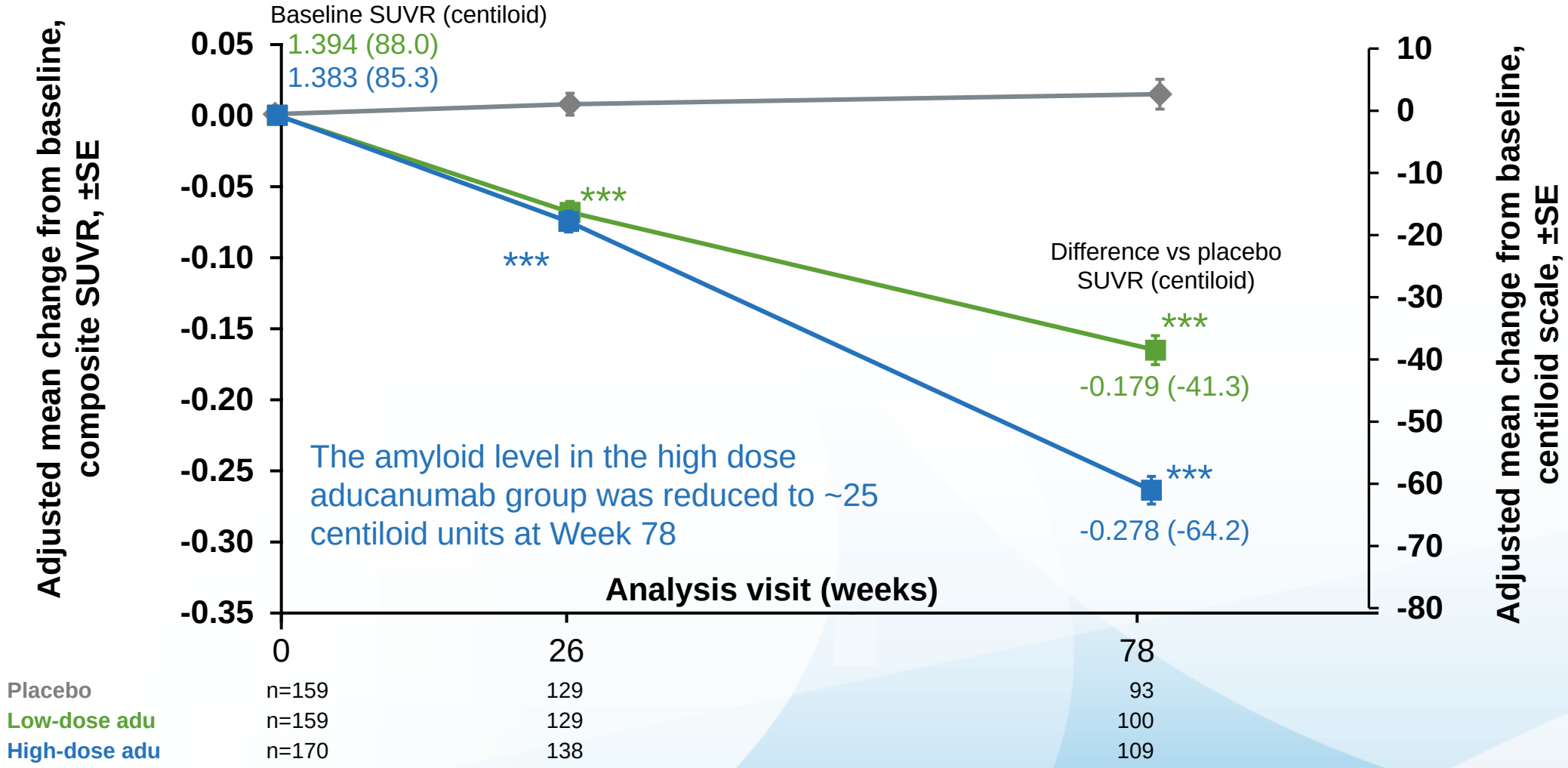
EMERGE: Amyloid PET showed dose- and time-dependent reduction in β-amyloid pathology with aducanumab



Placebo	n=159	129	93
Low-dose adu	n=159	129	100
High-dose adu	n=170	138	109

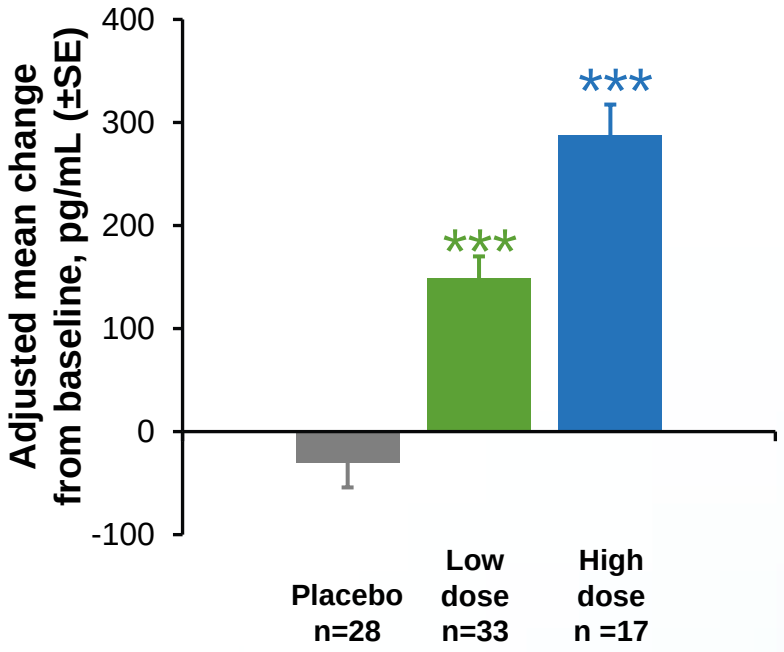
^{18}F-florbetapir amyloid PET analysis population. ***p<0.0001 compared with placebo (nominal). Values at each time point were based on an MMRM model, with change from baseline in MMSE as the dependent variable and with fixed effects of treatment group, categorical visit, treatment-by-visit interaction, 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.

EMERGE: CSF biomarkers of Alzheimer's disease and downstream pathology were impacted by aducanumab treatment

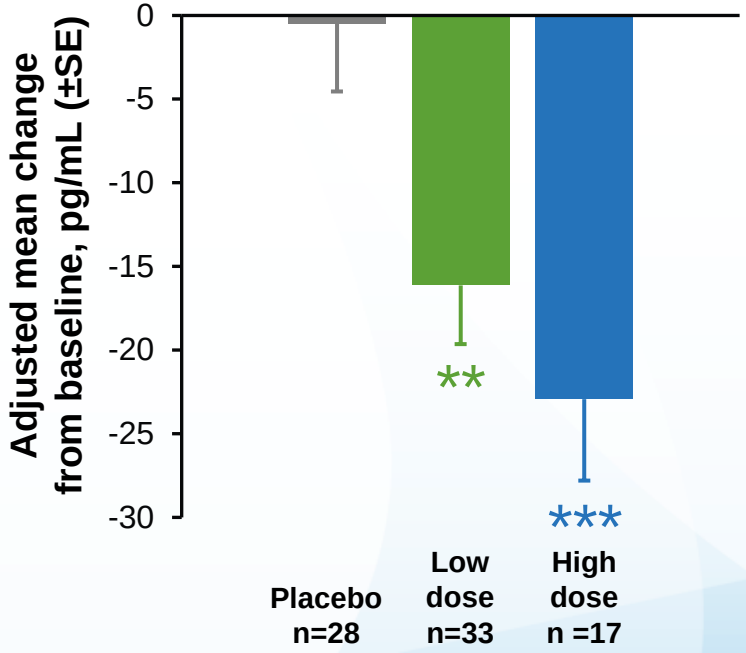
$A\beta_{1-42}$

Anti-amyloid target engagement, pathophysiology of Alzheimer's disease



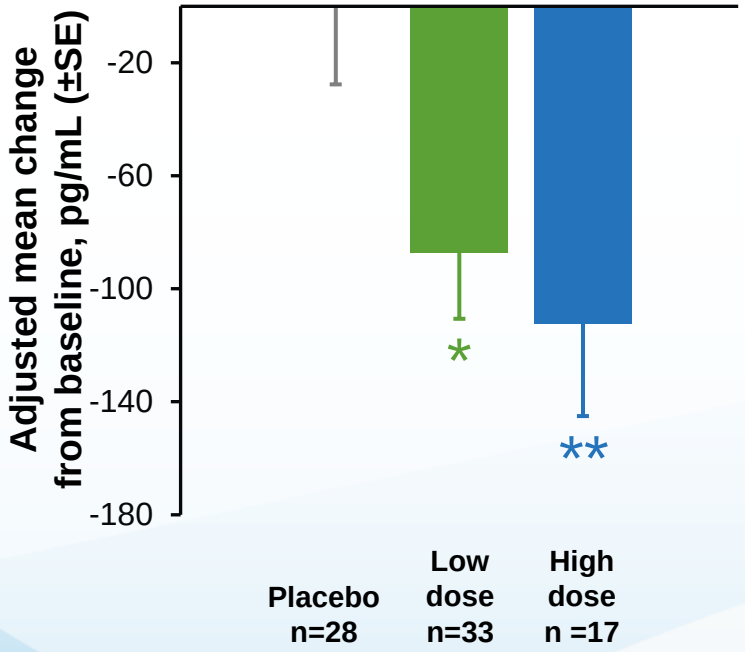
p-tau

Pathophysiology of Alzheimer's disease



t-tau

Neurodegeneration



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; CSF, cerebrospinal fluid; p-tau, phosphorylated tau 181; SE, standard error; t-tau, total tau.

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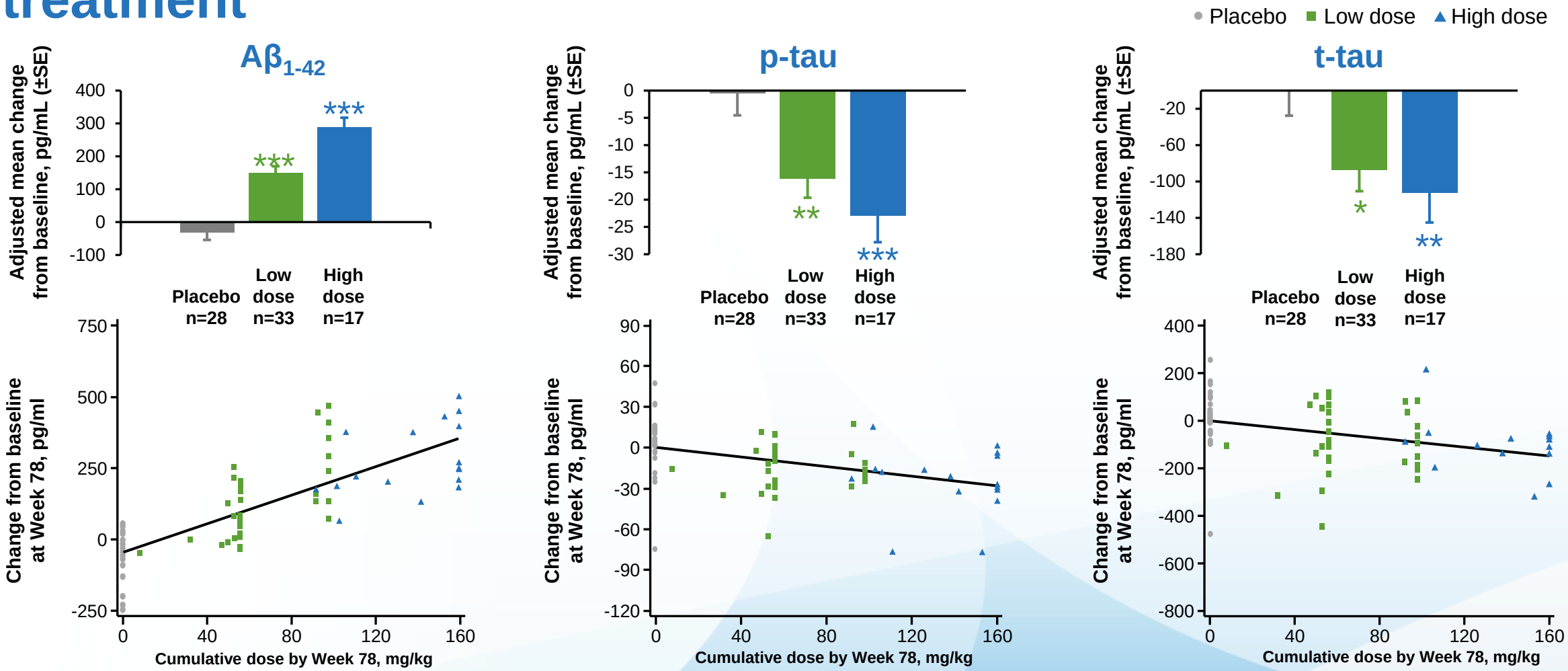

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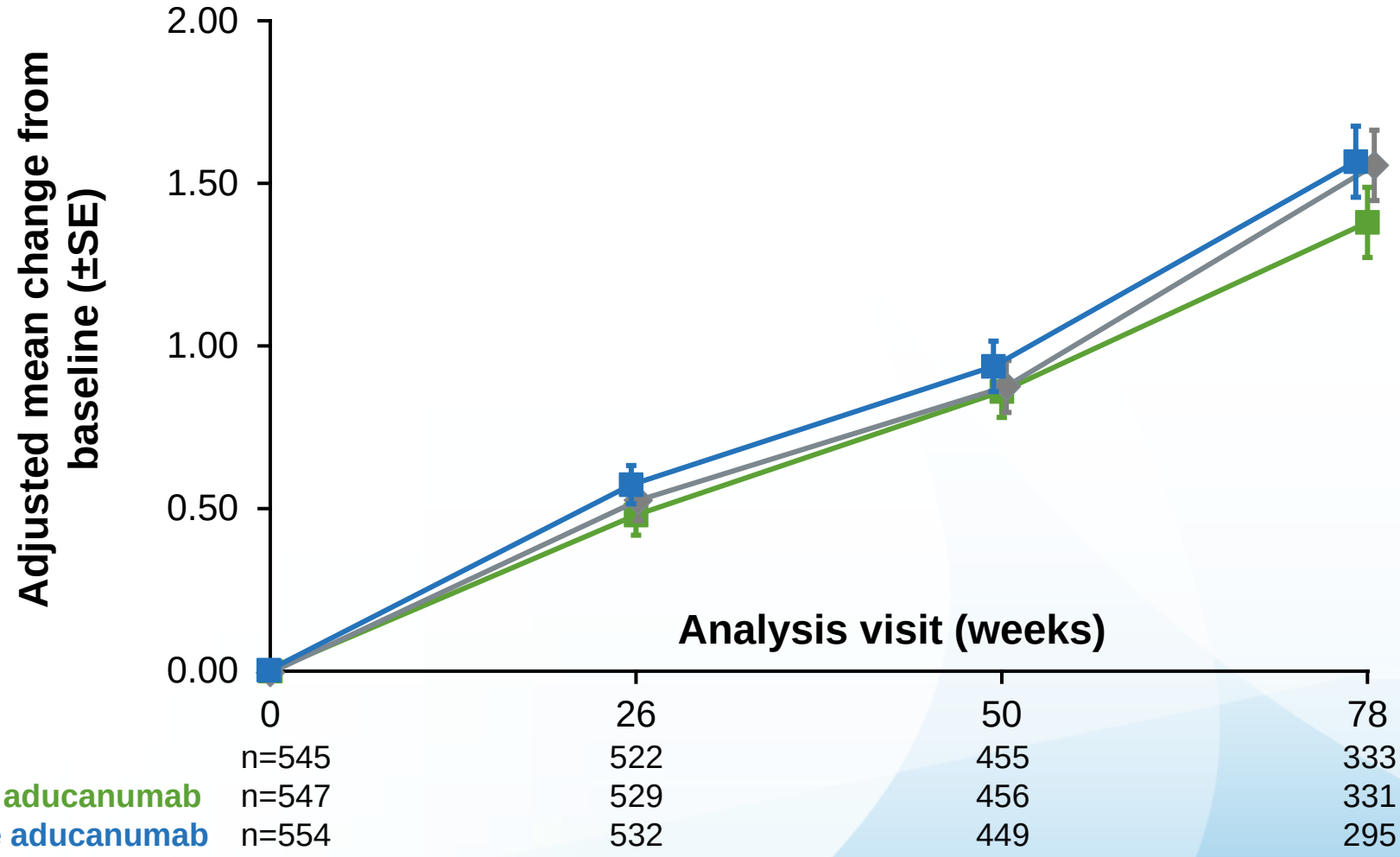
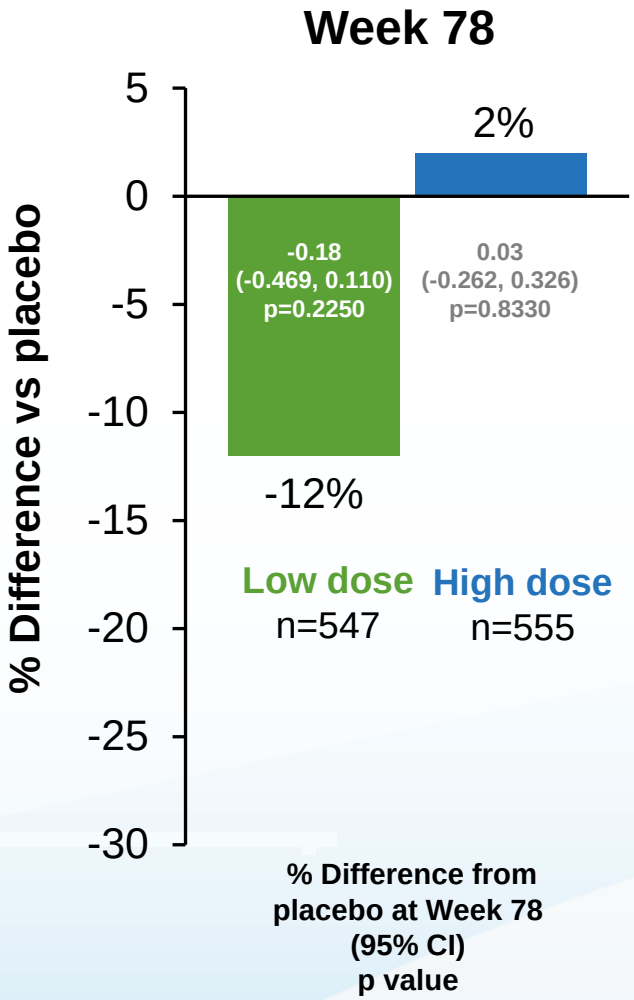
ENGAGE: Longitudinal change from baseline in CDR-SB

The primary endpoint of change from baseline in CDR-SB at Week 78 was not met



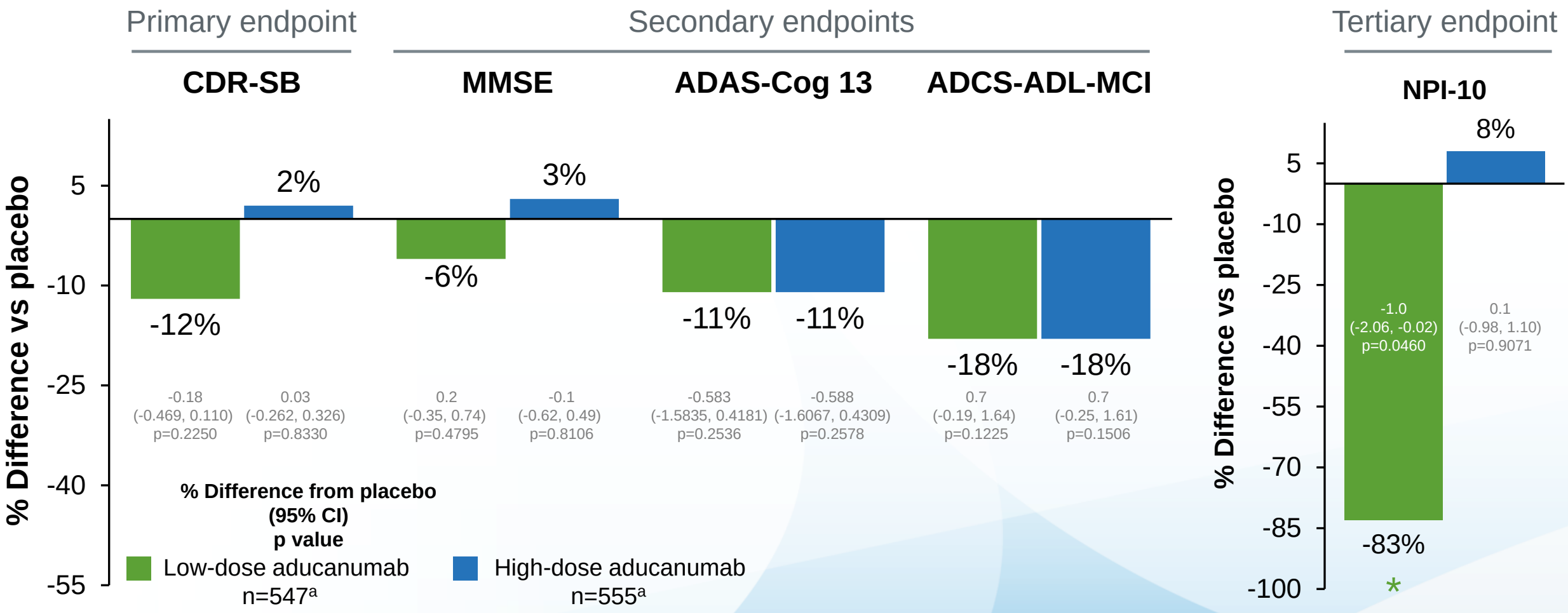


ITT population. Values at each time point were based on an MMRM model, with change from baseline in CDR-SB as the dependent variable and with fixed effects of treatment group, categorical visit, treatment-by-visit interaction, baseline CDR-SB, baseline CDR-SB by visit interaction, baseline MMSE, Alzheimer's disease symptomatic medication use at baseline, region, and laboratory ApoE ε4 status.

ApoE, apolipoprotein E; CDR-SB, Clinical Dementia Rating–Sum of Boxes; CI, confidence interval; ITT, intent to treat; MMRM, mixed model for repeated measure; MMSE, Mini Mental State Examination; SE, standard error.

ENGAGE: Clinical endpoints at Week 78

Results of the ENGAGE study were partially discordant with those of EMERGE



ITT population. *p <0.05 with placebo (nominal for NPI-10). [a]n=numbers of randomized and dosed participants included in the analysis.
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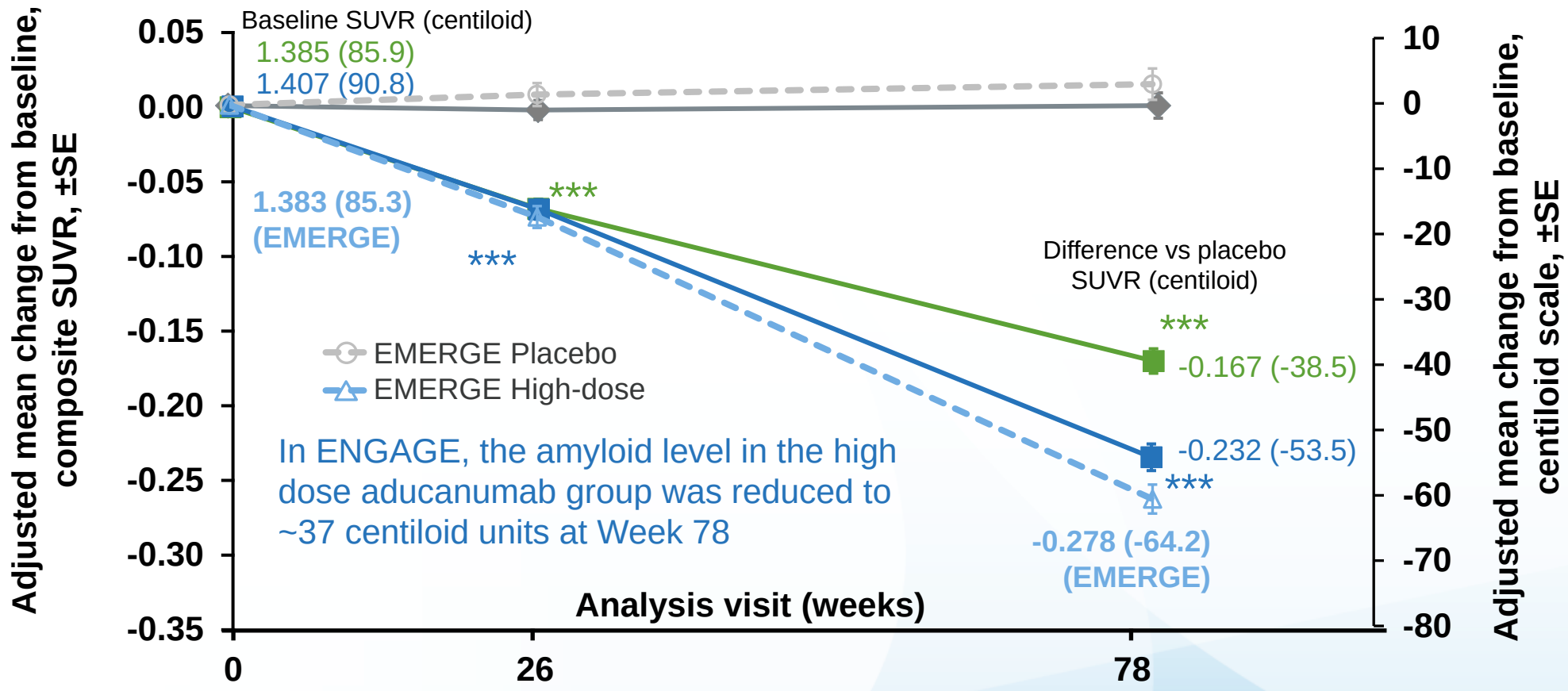
ENGAGE: Amyloid PET showed dose- and time-dependent reduction in β-amyloid pathology with aducanumab



Placebo	n=204	168	124
Low-dose adu	n=198	169	138
High-dose adu	n=183	156	112

Mean cumulative dose at Week 78:

ENGAGE
109.1 mg/kg

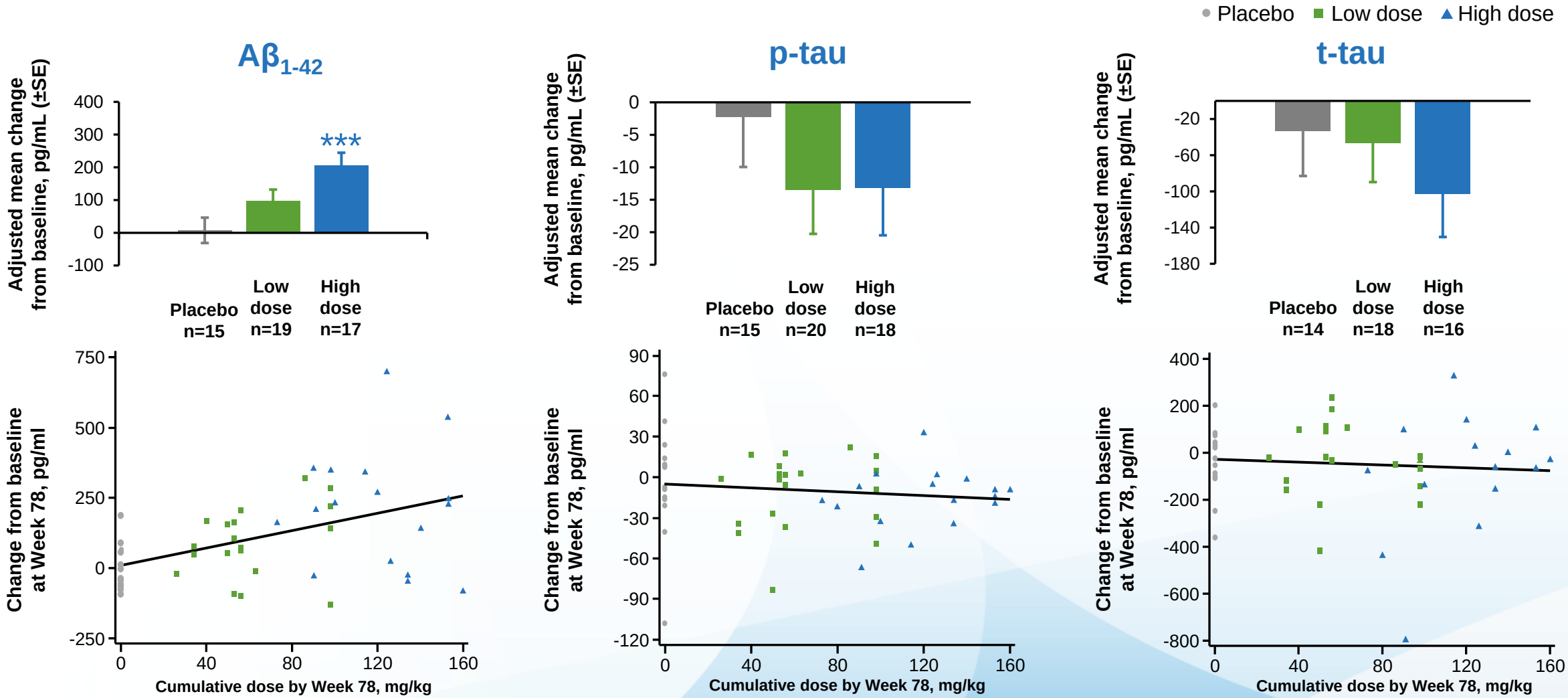
EMERGE
118.3 mg/kg

The magnitude of treatment effect observed in ENGAGE high dose (-0.232) is 16.5% less than that observed in EMERGE high dose (-0.278)

^{18}F-florbetapir amyloid PET analysis population. ***p<0.0001 compared with placebo (nominal). Values at each time point were based on an MMRM model, 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.

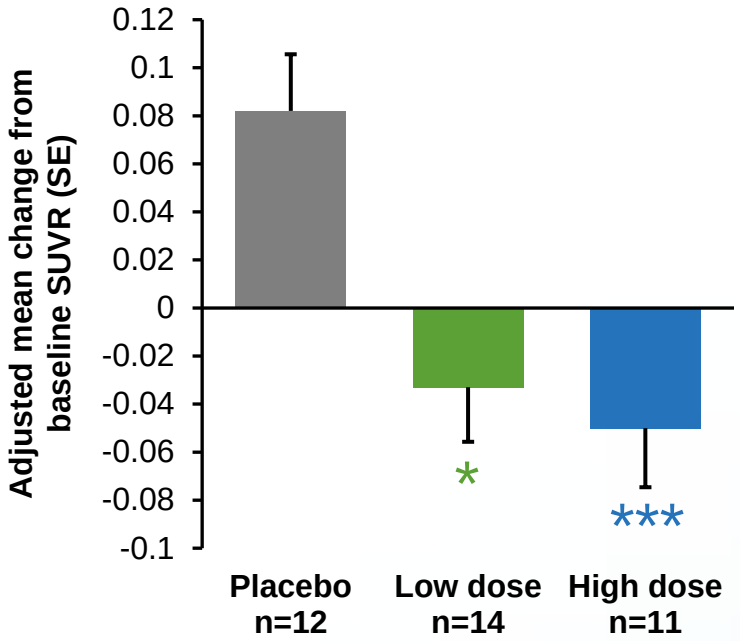
The effect of high-dose aducanumab CSF biomarkers in ENGAGE was less than in EMERGE



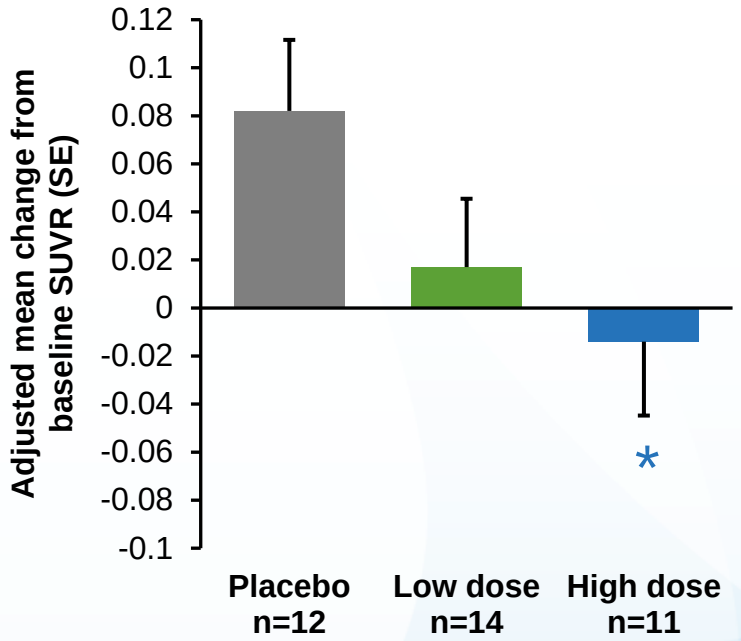
***p <0.001 compared with placebo (nominal).
Aβ, amyloid beta; CSF, cerebrospinal fluid; p-tau, phosphorylated tau 181;SE, standard error; t-tau, total tau.

EMERGE & ENGAGE: Aducanumab reduced tau pathophysiology, as measured by MK-6420 tau PET

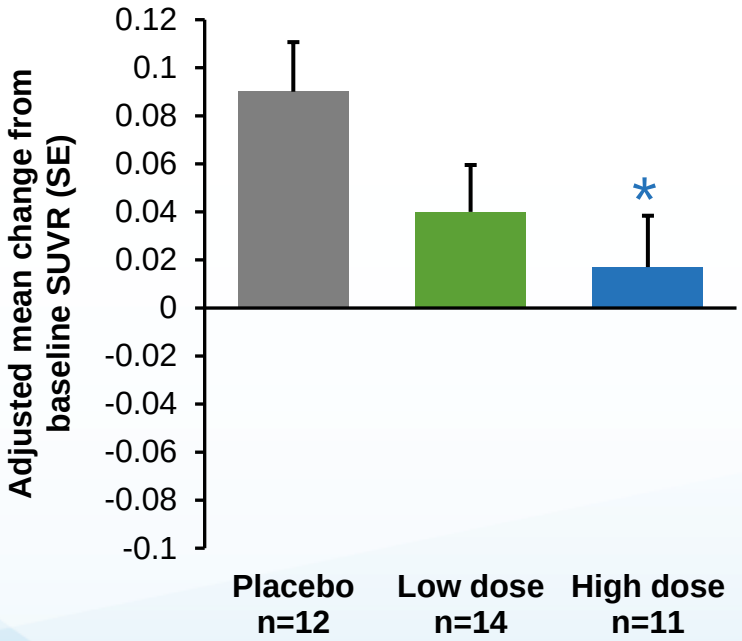
Medial temporal composite



Temporal composite

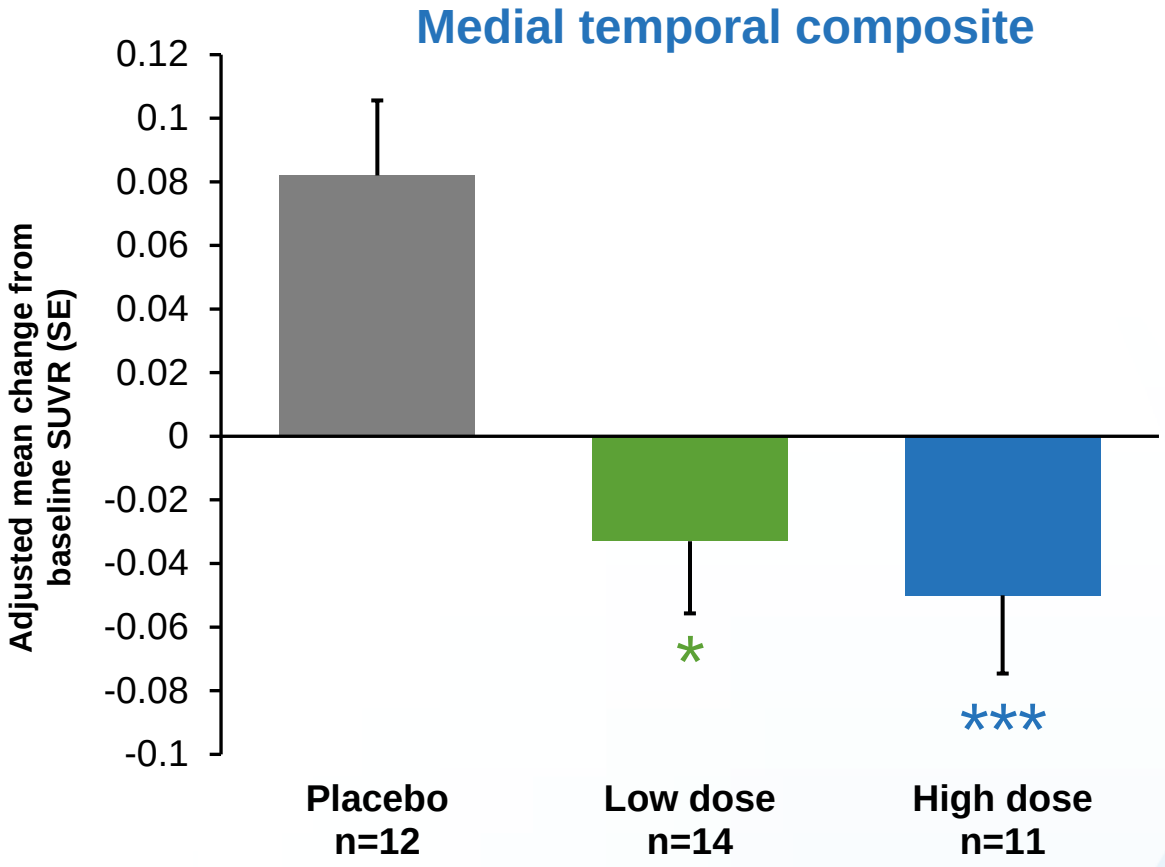


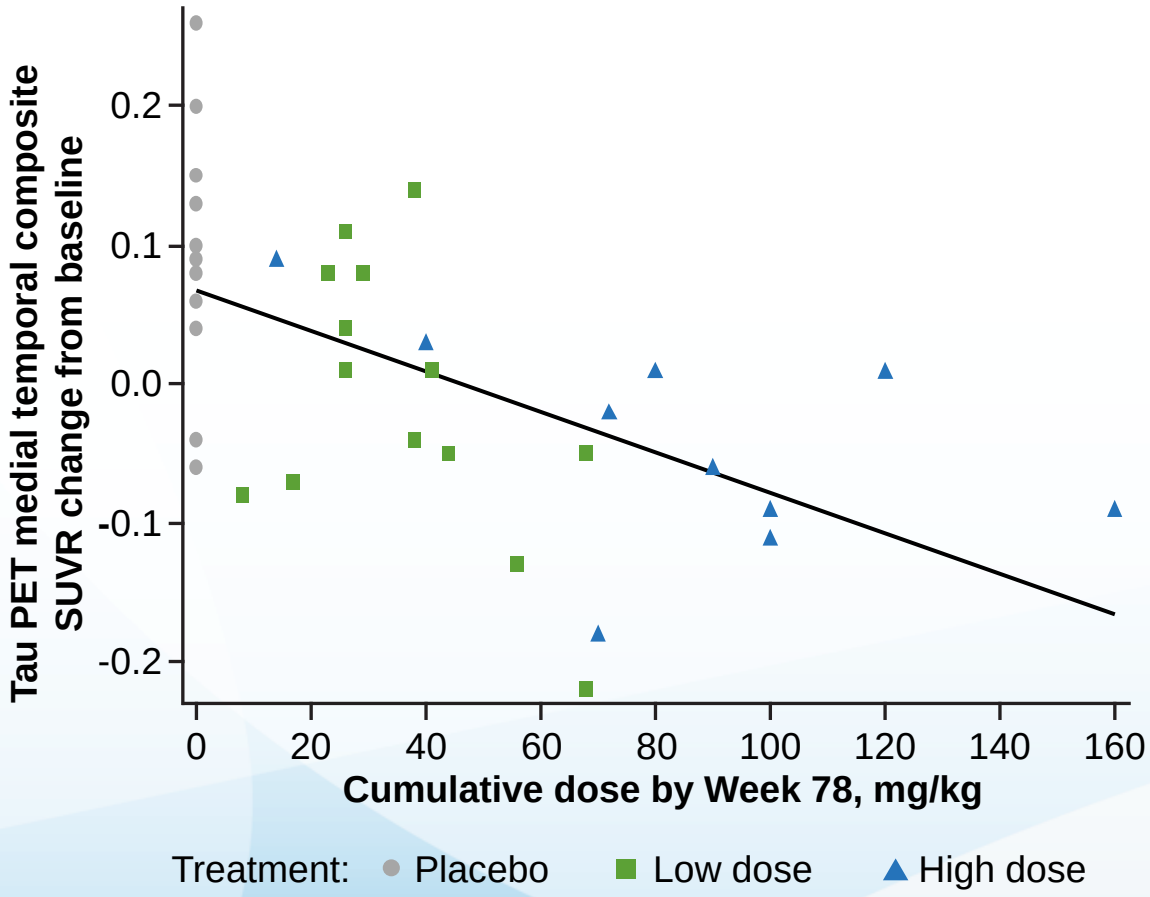
Frontal composite



Pooled tau PET analysis population. ^{18}F-MK6240 Tau PET tracer. *p<0.05; ***p<0.0001 compared with placebo (nominal).
PET, positron emission tomography; SE, standard error; SUVR, standardized uptake value ratio.

Higher cumulative dose of aducanumab was correlated with a greater reduction in MK-6420 tau PET signal





Pooled tau PET analysis population. *p<0.05; ***p<0.0001 compared with placebo (nominal).
PET, positron emission tomography; SE, standard error; SUVR, standardized uptake value ratio.

EMERGE, ENGAGE, and PRIME results were largely consistent, excepting the high-dose aducanumab group from ENGAGE

Diff vs Placebo (%)	Low-dose aducanumab		High-dose aducanumab		PRIME
	ENGAGE N=547	EMERGE N=543	ENGAGE N=555	EMERGE N=547	10 mg/kg N=32
CDR-SB	-0.18 (-12%)	-0.26 (-15%)	0.03 (2%)	**-0.39 (-22%)**	**-1.26 (-67%)**
MMSE	0.2 (-6%)	-0.1 (3%)	-0.1 (3%)	**0.6 (-18%)**	**1.9 (-76%)**
ADAS-Cog 13	-0.58 (-11%)	-0.70 (-14%)	-0.59 (-11%)	**-1.40 (-27%)**	
ADCS-ADL-MCI	0.7 (-18%)	0.7 (-16%)	0.7 (-18%)	**1.7 (-40%)**	
Amyloid-PET* SUVR (centiloid unit)	**-0.167 (-38.5)**	**-0.179 (-41.3)**	**-0.232 (-53.5)**	**-0.278 (-64.2)**	**-0.277 (-61.1)**

p<0.05 favoring aducanumab

Numeric advantage favoring aducanumab

No numeric advantage favoring aducanumab

N=numbers of randomized and dosed participants.
* Number of participants in ENGAGE PET substudy = 585 and EMERGE substudy = 488.
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; CI, confidence interval; MMSE, Mini-Mental State Examination; PET, positron emission tomography; SUVR, standardized uptake value ratio.

The partially discordant results between EMERGE and ENGAGE were extensively investigated

- Demographics, disease characteristics, frequency, severity and management of ARIA were all similar between studies
- Underlying pharmacology of aducanumab is similar in ENGAGE and EMERGE
- Differences between studies were largely driven by:
  - Lower exposure to 10 mg/kg dosing in ENGAGE
  - Imbalance in number and distribution of rapid progressing Alzheimer's disease patients

In ENGAGE, patients randomized to groups with the opportunity for full 10 mg/kg dosing had results similar to EMERGE

ARIA, amyloid-related imaging abnormalities.

No evidence of functional unblinding from ARIA management was observed across clinical scales

Differences vs placebo with respect to primary and secondary endpoints were compared using:

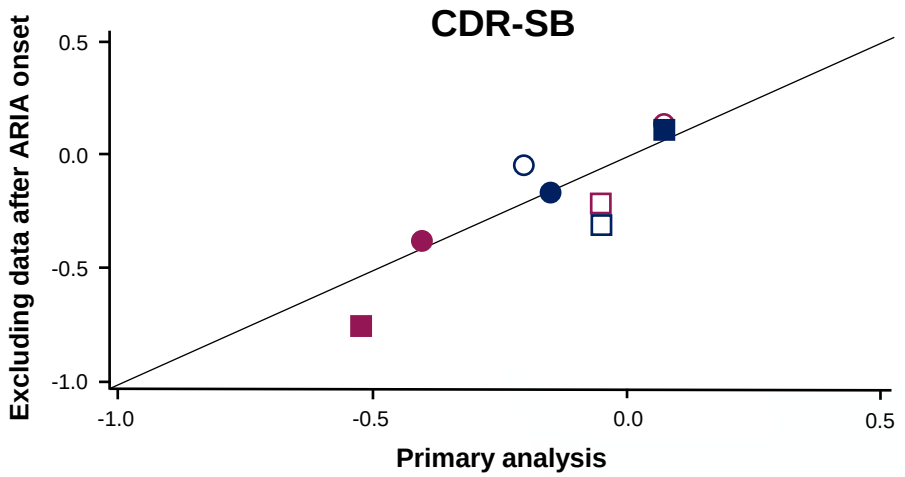
- primary analysis (**x-axis**)
- analysis excluding data after ARIA onset (**y-axis**)

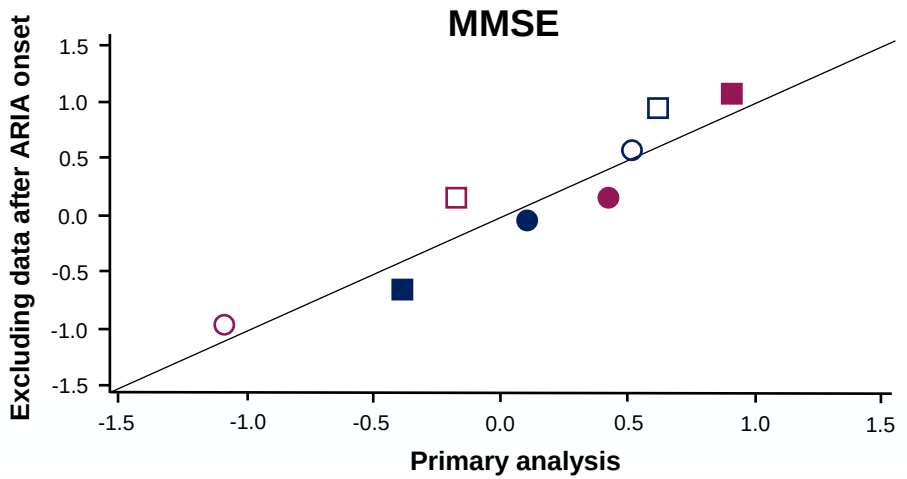
Results show that data points are **scattered evenly above and below** the line of unity, indicating random variability and no evidence of functional unblinding

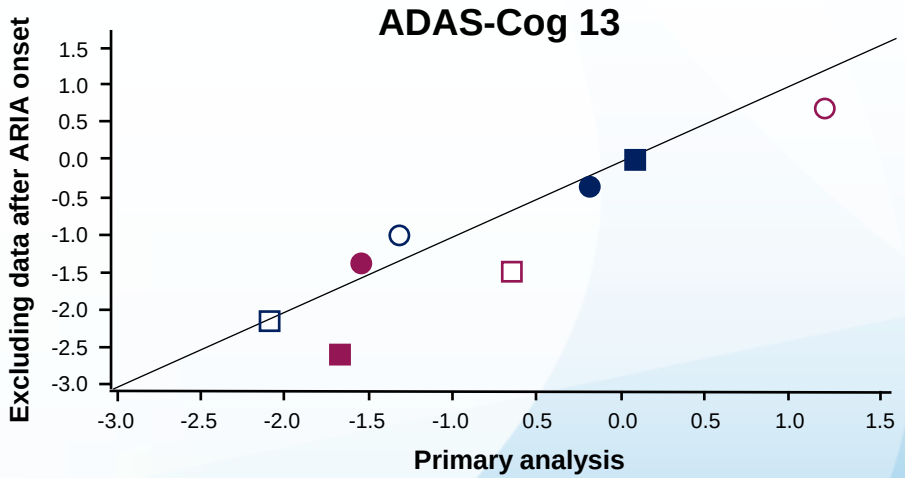
EMERGE **ENGAGE**

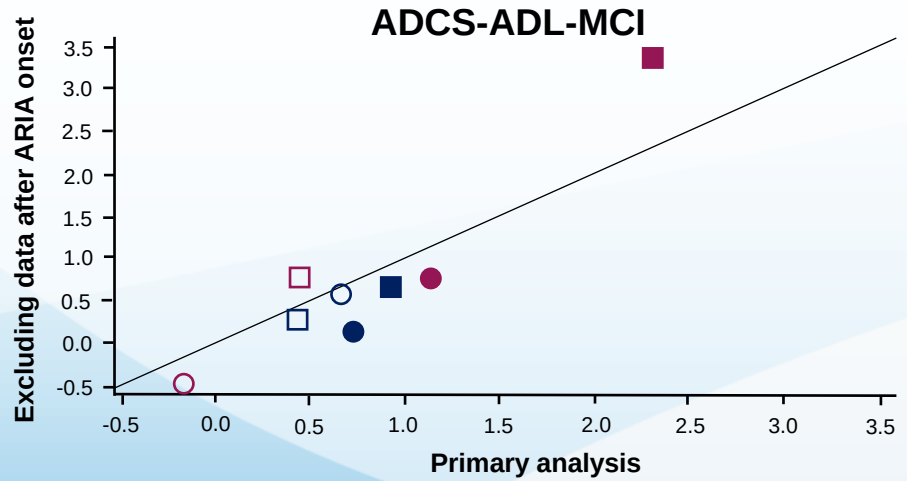
■ high dose carrier □ high dose non-carrier

● low dose carrier ○ low dose non-carrier





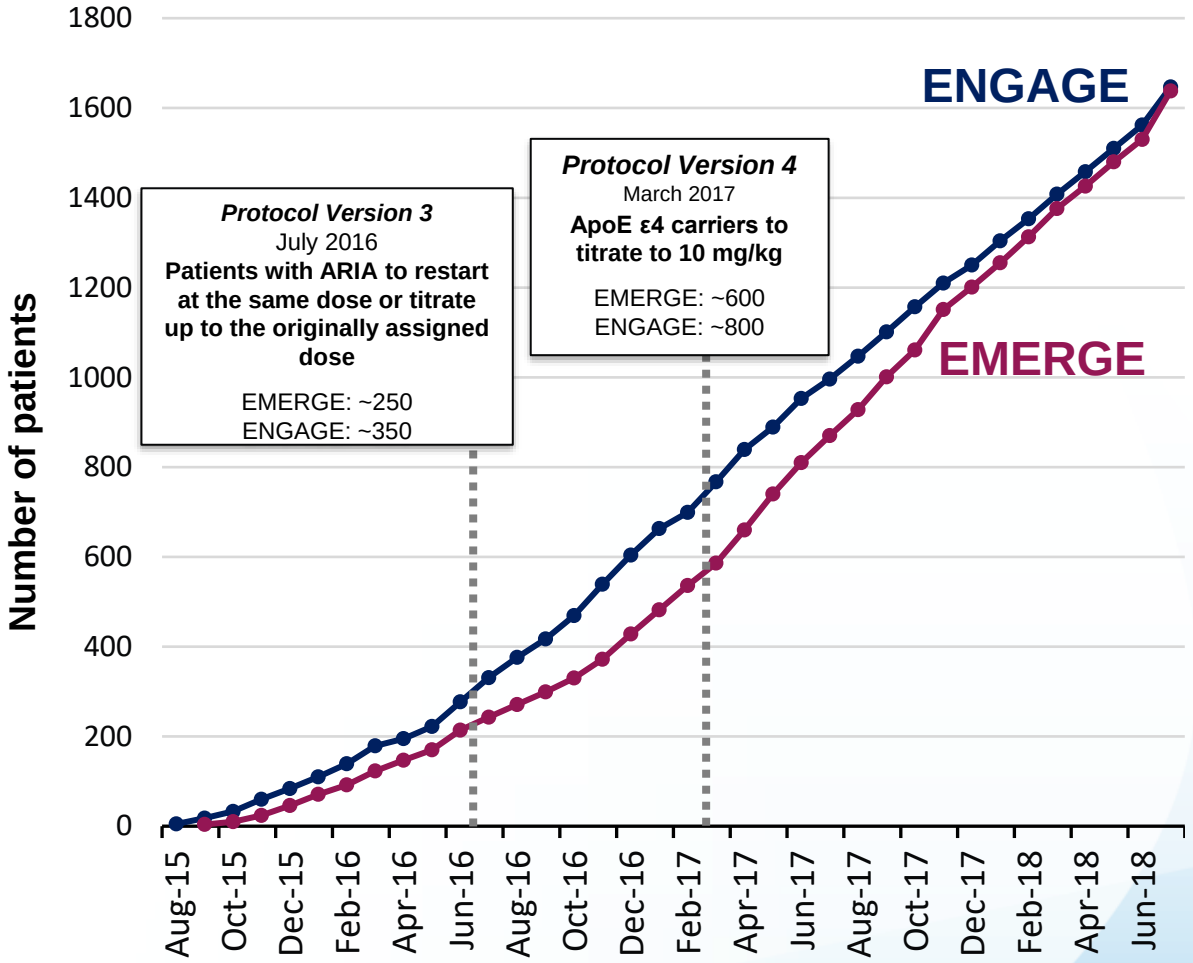


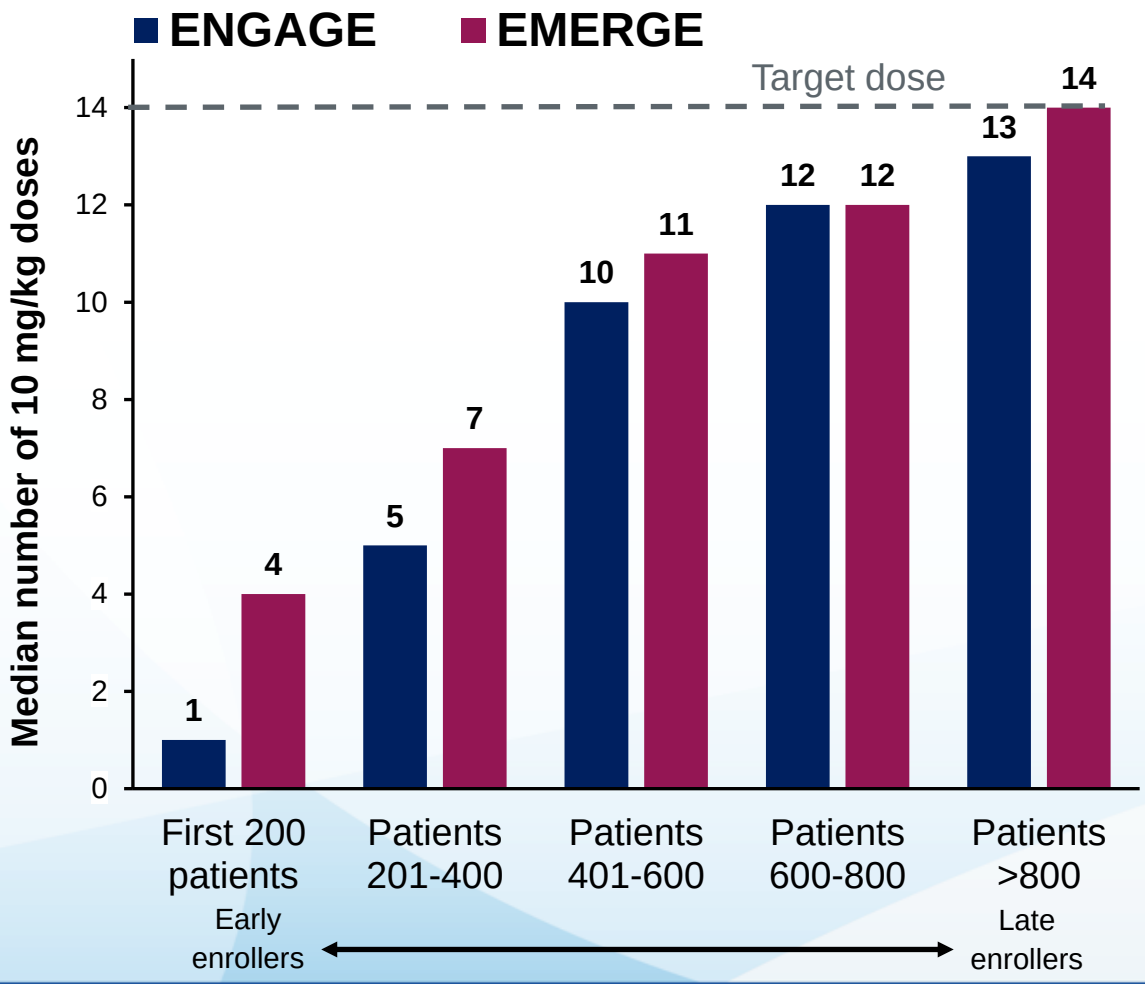


ARIA, amyloid-related imaging abnormalities; ADAS-Cog 13, Alzheimer's Disease Assessment Scale–Cognitive Subscale (13-item); ADCS-ADL-MCI, Alzheimer's Disease Cooperative Study–Activities of Daily Living Inventory (mild cognitive impairment version); CDR-SB, Clinical Dementia Rating–Sum of Boxes; MMSE, Mini-Mental State Examination.

Differences in study enrollment and implementation of protocol amendments reduced exposure to 10 mg/kg

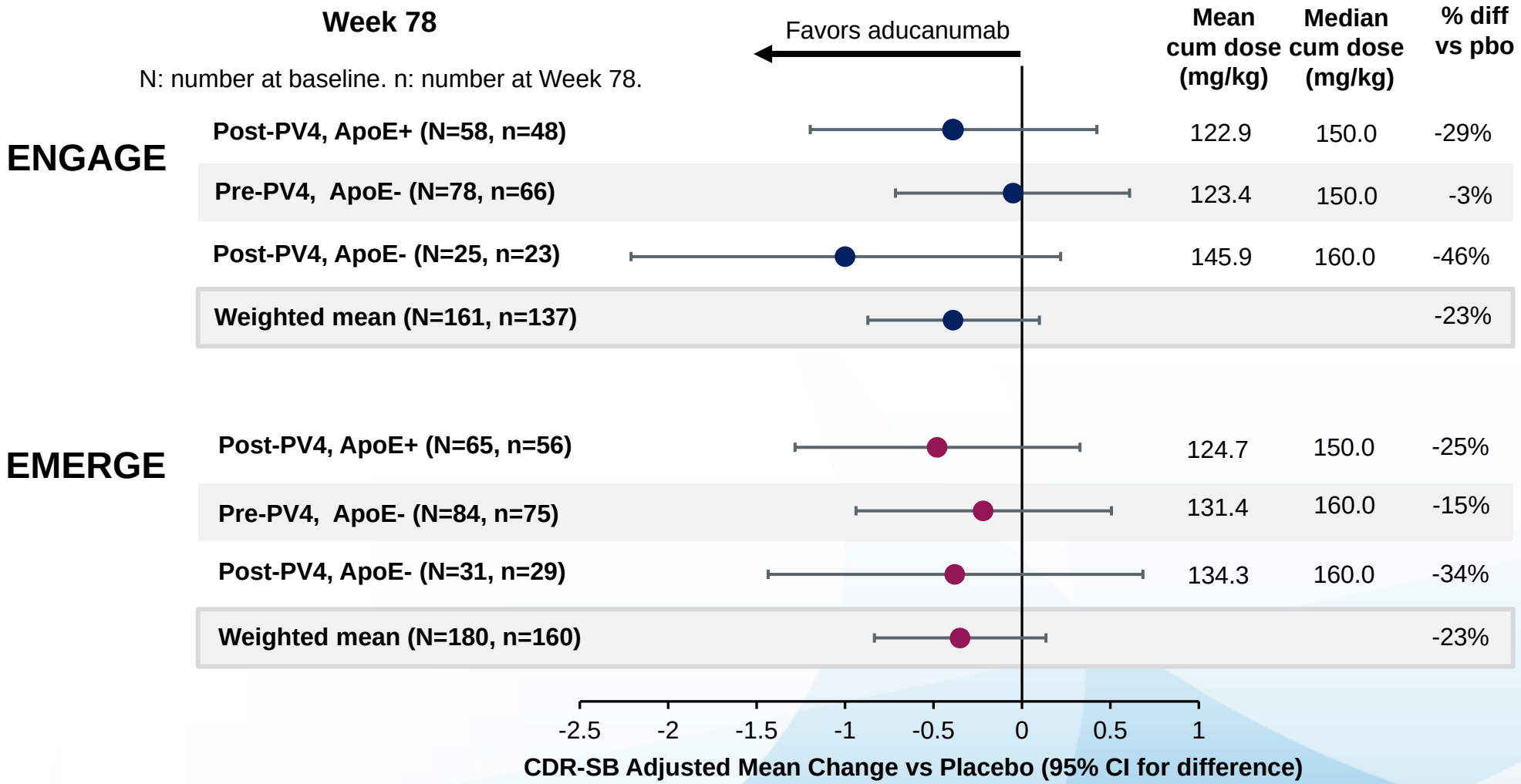
Early enrolled patients had lower exposure to 10 mg/kg





ApoE, apolipoprotein E; ARIA, amyloid related imaging abnormalities.

Patients who had the opportunity for 14 doses of 10 mg/kg had similar benefit in both studies

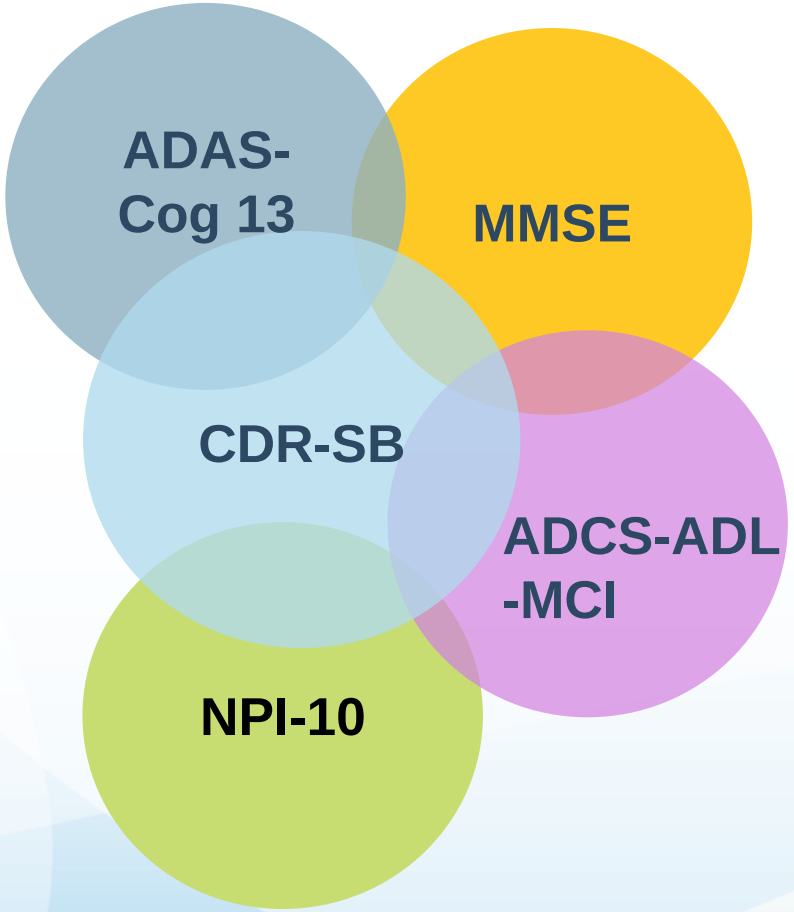


Patients who have had the opportunity to complete week 78 visit by 20 March 2019.
ApoE, apolipoprotein E; pbo, placebo; CDR-SB, Clinical Dementia Rating Scale–Sum of Boxes; CI, confidence interval; pbo, placebo, PV4, protocol amendment version 4.

Clinical endpoints measure distinct, important symptoms of cognition, function, and behavior

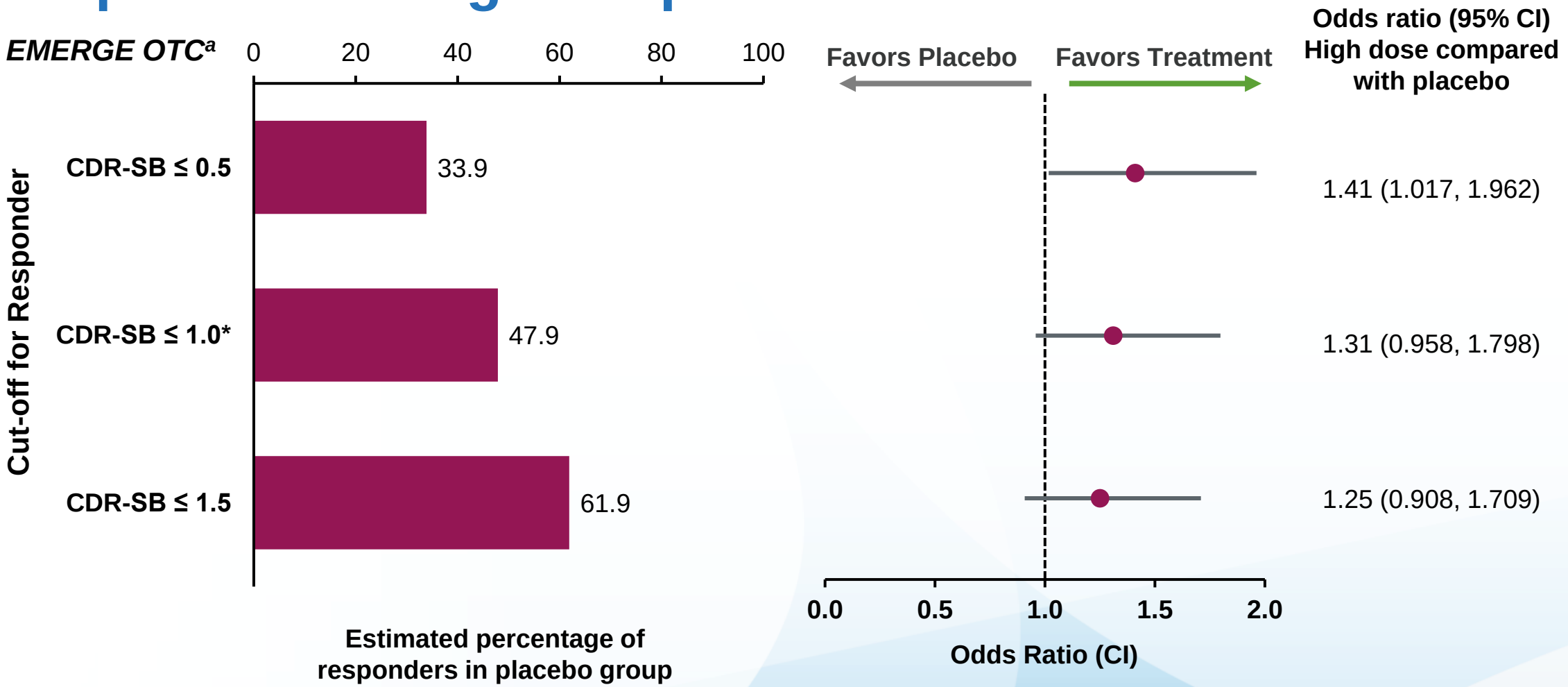
Five clinical rating scales were used in EMERGE and ENGAGE

- Validated and widely used in early Alzheimer's disease
- Includes key perspectives:
  - Expert clinical judgements based on patient examination and caregiver input
  - Patient and caregiver reports
  - Cognitive performance tests
- Collectively they cover the full scope of symptoms experienced by patients with Alzheimer's disease with minimal overlap



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, Clinical Dementia Rating–Sum of Boxes; MMSE, Mini-Mental State Examination; NPI-10, Neuropsychiatric Inventory (10-item).

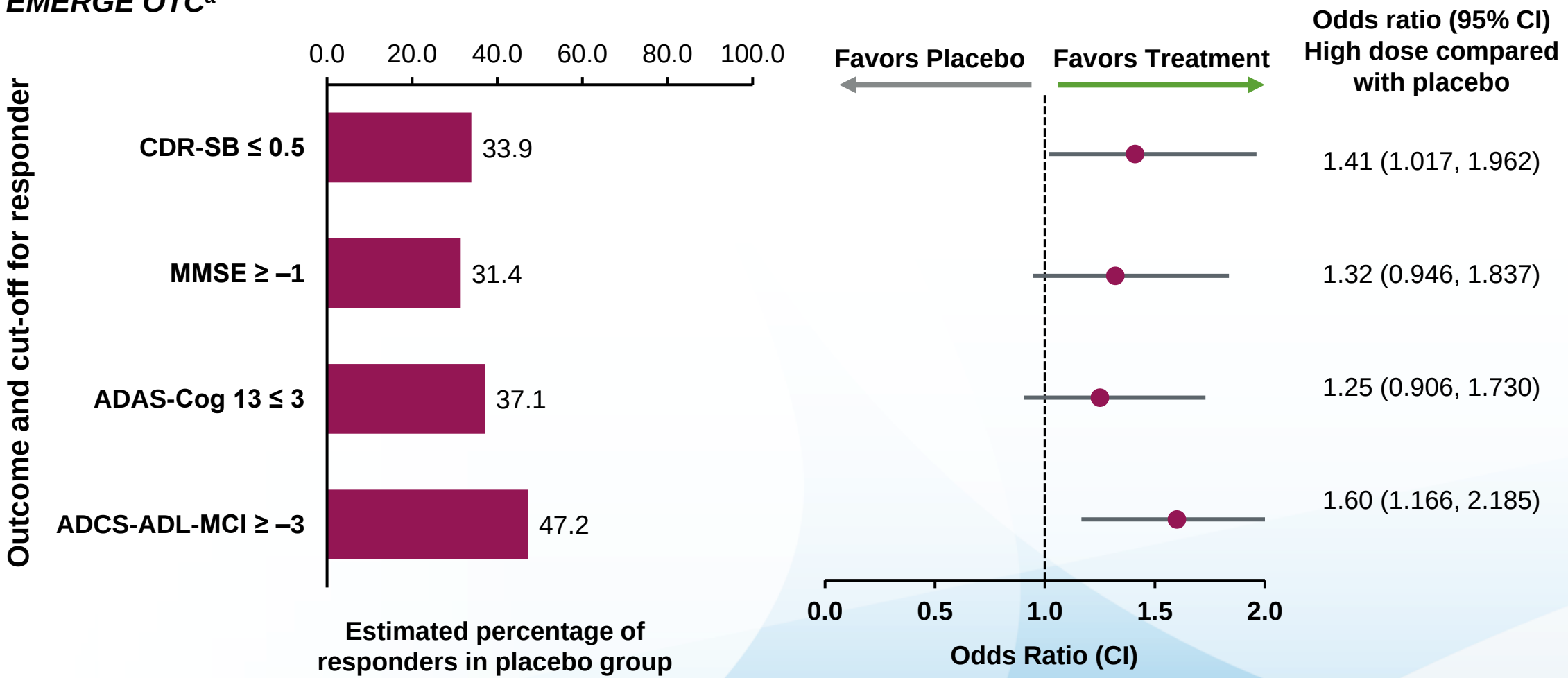
High-dose aducanumab increased the percentage of responders using multiple thresholds



[a] Patients with missing values at Week 78 were classified as non-responders.
* CDR-SB ≤ 1.0 was post hoc analysis.
CDR-SB, Clinical Dementia Rating Scale–Sum of Boxes; CI, confidence interval; OTC, opportunity to complete.

High-dose aducanumab improved response vs placebo across clinical endpoints

EMERGE OTC[a]

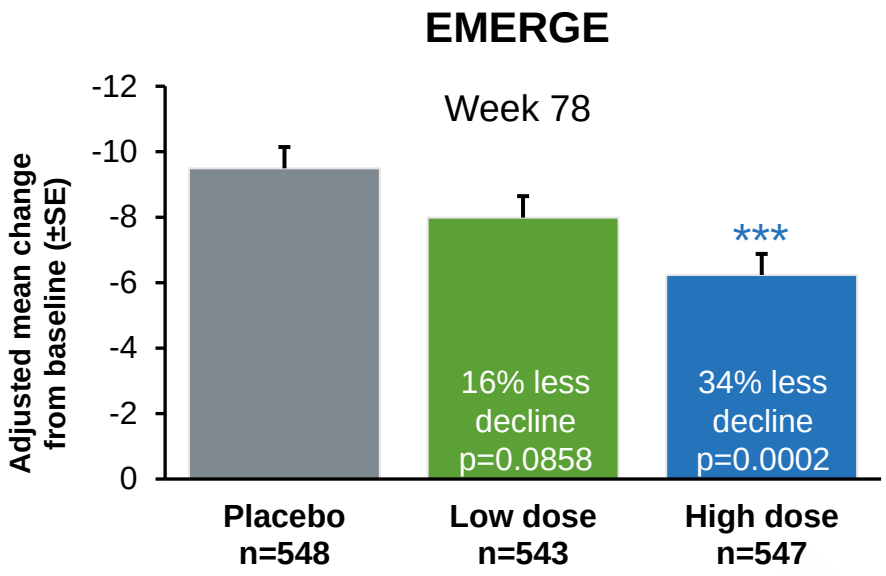


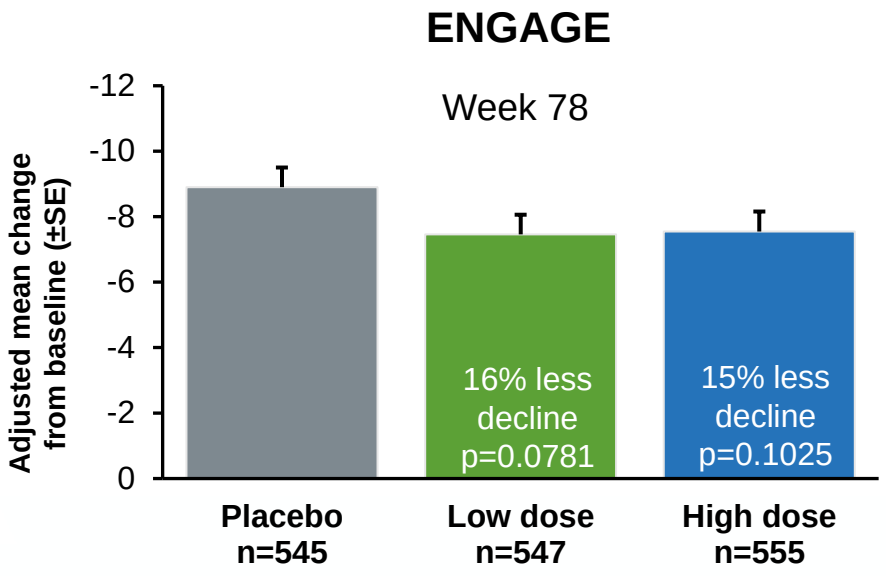
[a] Patients with missing values at Week 78 were classified as non-responders. Responder threshold defined as worsening ≤ 0.5 baseline SD.
ADAS-Cog 13, Alzheimer's Disease Assessment Scale–Cognitive Subscale (13-item); ADCS-ADL-MCI, Alzheimer's Disease Cooperative Study–Activities of Daily Living Inventory (mild cognitive impairment version); CDR-SB, Clinical Dementia Rating Scale–Sum of Boxes; CI, confidence interval; MMSE, Mini-Mental State Examination; OTC, opportunity to complete; SD, standard deviation.

Composite measures were consistent with primary analyses

iADRS-like endpoint

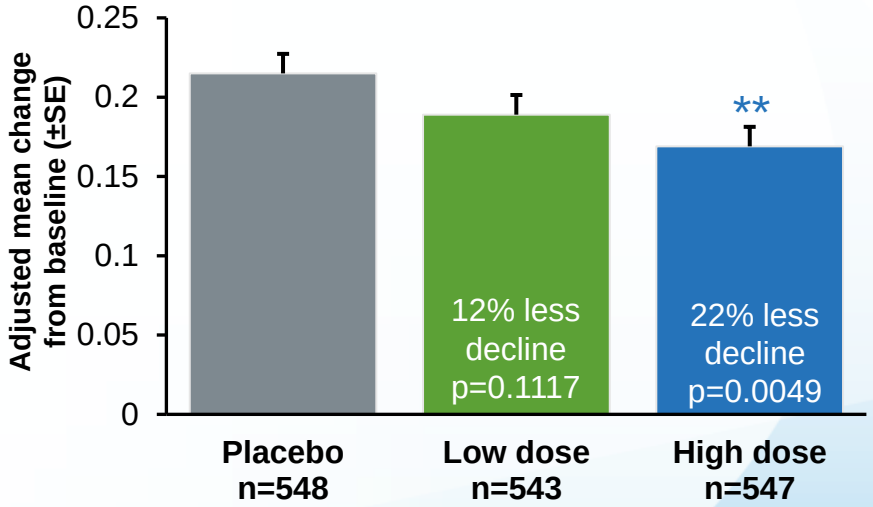
Composite results based on total scores of ADAS-Cog13 and ADCS-ADL-MCI

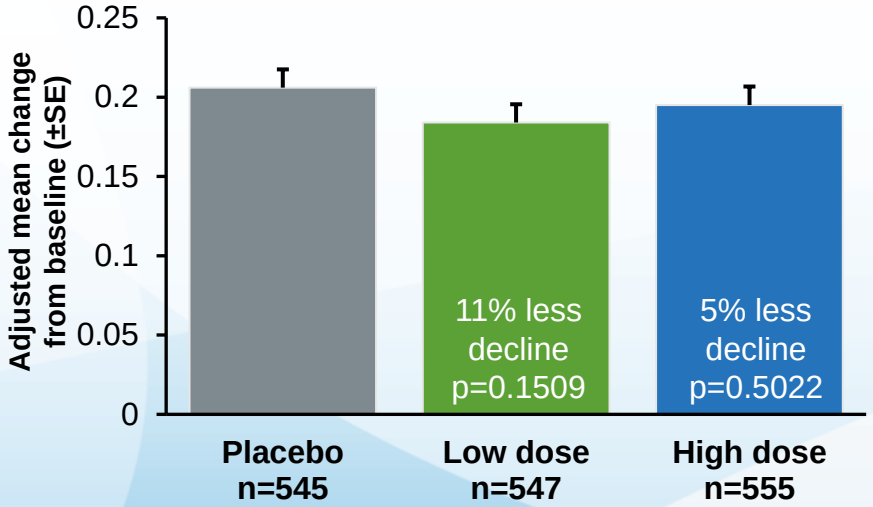




ADCOMS

Composite results based on selected items in ADAS-Cog13, MMSE and CDR-SB





n=numbers of randomized and dosed patients included in the analysis. **p <0.01, and ***p <0.001 compared with placebo (nominal).
ADAS-Cog 13, Alzheimer's Disease Assessment Scale–Cognitive Subscale (13-item); ADCOMS, Alzheimer's Disease Composite Score; ADCS-ADL-MCI, Alzheimer's Disease Cooperative Study–Activities of Daily Living Inventory (mild cognitive impairment version); CDR-SB, Clinical Dementia Rating Scale–Sum of Boxes; iADRS, The Integrated Alzheimer's Disease Rating Scale; MMSE, Mini-Mental State Examination; SE, standard error.

Aducanumab Phase 3 studies EMERGE and ENGAGE

- In EMERGE, high-dose aducanumab resulted in a consistent reduction of clinical decline across all 5 clinical endpoints spanning cognition, daily function and behavioral symptoms in patients with early Alzheimer's disease
  - Effects on amyloid PET and downstream biomarkers specific to Alzheimer's disease (CSF p-tau) and neurodegeneration (CSF t-tau) further support the clinical findings
- ENGAGE did not meet its primary endpoint
- The partially discordant results between EMERGE and ENGAGE were extensively investigated
  - Dose and unbalanced distribution of rapid progressors were the primary contributors to the discordant results observed between the two studies in the high dose aducanumab arm
  - Patients in ENGAGE who had the opportunity for 14 doses of 10 mg/kg had clinical efficacy consistent with EMERGE
- Post-hoc analyses of composite scales are reflective of the component scales, and consistent with the primary analyses

Aβ, amyloid beta; 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 Scale–Sum of Boxes; CSF, cerebrospinal fluid; PET, positron-emission tomography; p-tau, phosphorylated tau 181; t-tau, total tau.