EMERGE and ENGAGE Topline Results: Two Phase 3 Studies to Evaluate Aducanumab in Patients With Early Alzheimer's Disease

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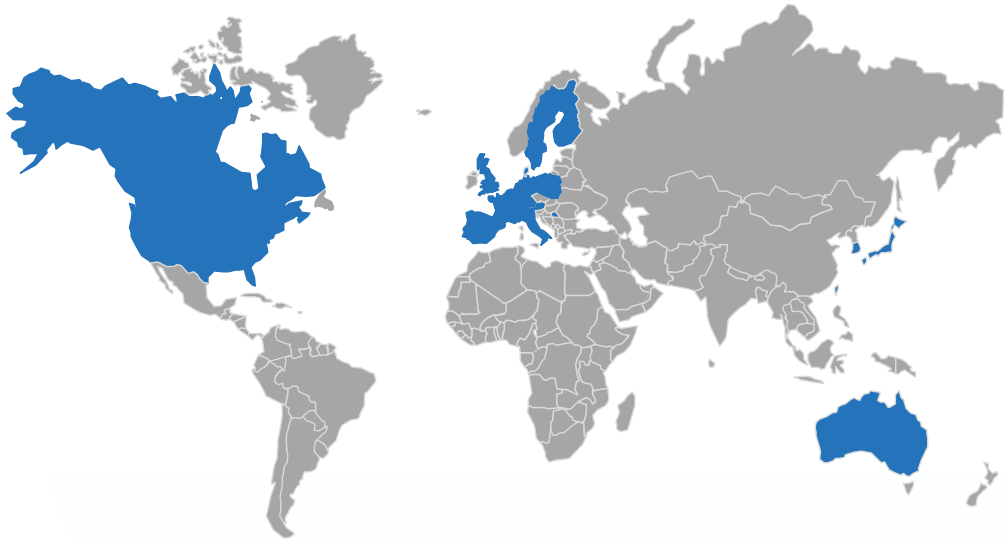
Legal disclaimer

- Aducanumab is an investigational compound and is not yet approved 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

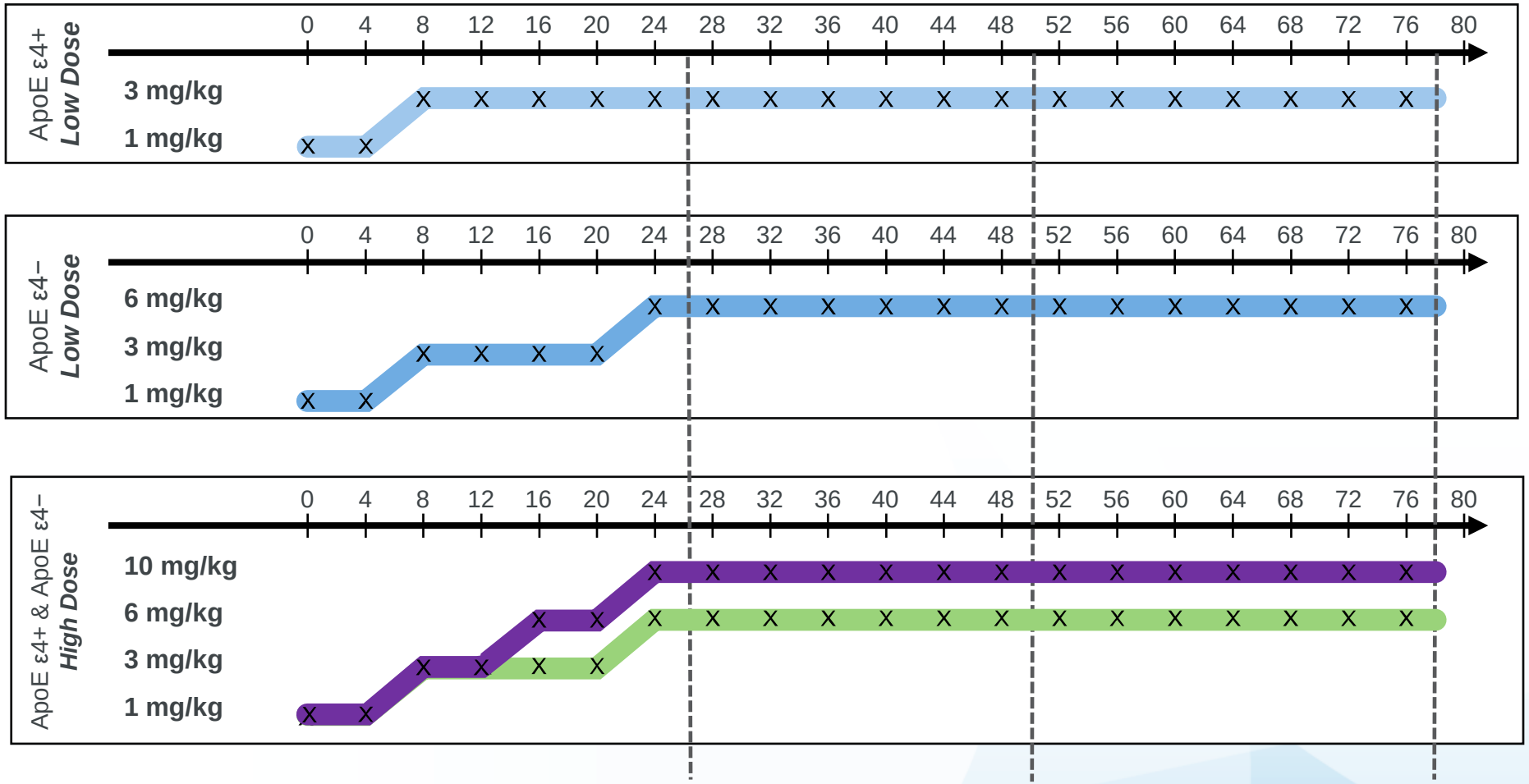
Studies	Two 18-month, randomized, double-blind, placebo-controlled, Phase 3 studies
Geography/ sample size	3285 patients at 348 sites in 20 countries
Population	▪ Early Alzheimer's disease (MCI due to Alzheimer's disease + mild Alzheimer's disease dementia) • MMSE 24-30, CDR-G 0.5, RBANS ≤ 85, with confirmed amyloid pathology
Doses	▪ Two dosing regimens (low and high) and placebo; randomized 1:1:1
Primary endpoint	▪ CDR-SB at 18 months
Other endpoints	▪ Secondary: MMSE, ADAS-Cog 13, ADCS-ADL-MCI ▪ 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

1. ClinicalTrials.gov: https://clinicaltrials.gov/ct2/show/NCT02477800. Accessed November 2019; ClinicalTrials.gov: https://clinicaltrials.gov/ct2/show/NCT02484547. Accessed November 2019; Data on file.
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; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; PET, positron-emission tomography; RBANS, Repeatable Battery for Assessment of Neuropsychological Status.

EMERGE and ENGAGE: Dose regimen



- Low dose titrated to 3 or 6 mg/kg
- Maintained throughout study

- High dose titrated to 6 or 10 mg/kg for Protocol Versions 1-3
- High dose titrated to 10 mg/kg for Protocol Version 4 and higher

Expected # of 10 mg/kg in high dose group ***by Week 26*: 1 dose** ***by Week 50*: 7 doses** ***by Week 78*: 14 doses**

ApoE, apolipoprotein E.

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±7.40	70.6±7.45	70.6±7.47	69.8±7.72	70.4±6.96	70.0±7.65
Female, n (%)	290 (52.9)	269 (49.5)	284 (51.9)	287 (52.7)	284 (51.9)	292 (52.6)
Race, n (%) Asian White	 47 (8.6) 415 (75.7)	 38 (7.0) 418 (77.0)	 41 (7.5) 405 (74.0)	 55 (10.1) 413 (75.8)	 55 (10.1) 412 (75.3)	 65 (11.7) 413 (74.4)
Education years, mean ± SD	14.5±3.82	14.5±3.63	14.6±3.74	14.7±3.66	14.6±3.77	14.6±3.72
Alzheimer's disease medications used, n (%)	279 (50.9)	277 (51.0)	277 (50.6)	293 (53.8)	307 (56.1)	307 (55.3)
ApoE ε4, n (%) Carriers Non-carriers	 367 (67.0) 178 (32.5)	 362 (66.7) 178 (32.8)	 365 (66.7) 181 (33.1)	 376 (69.0) 167 (30.6)	 391 (71.5) 156 (28.5)	 378 (68.1) 176 (31.7)
Clinical stage, n (%) MCI due to Alzheimer's disease Mild Alzheimer's disease	 446 (81.4) 102 (18.6)	 452 (83.2) 91 (16.8)	 438 (80.1) 109 (19.9)	 443 (81.3) 102 (18.7)	 440 (80.4) 107 (19.6)	 442 (79.6) 113 (20.4)
Amyloid PET SUVR, mean composite ± SD (n) *PET sub-study population only*	1.37±0.175 (157)	1.39±0.181 (157)	1.38±0.183 (171)	1.38±0.198 (203)	1.39±0.186 (198)	1.41±0.177 (18

ITT population.

ApoE, apolipoprotein E; ITT, intent to treat; MCI, mild cognitive impairment; PET, positron-emission tomography; SD, standard deviation; SUVR, standardized uptake value ratio.

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±14.23	60.0±14.02	60.7±14.15	60.0±13.65	59.5±14.16	60.6±14.09
MMSE score, mean ± SD	26.4±1.78	26.3±1.72	26.3±1.68	26.4±1.73	26.4±1.78	26.4±1.77
CDR global score, n (%) 0.5 1	 544 (99.3) 3 (0.5)	 543 (100) 0	 546 (99.8) 1 (0.2)	 544 (99.8) 1 (0.2)	 546 (99.8) 1 (0.2)	 554 (99.8) 0
CDR-SB score, mean ± SD	2.47±0.999	2.46±1.011	2.51±1.053	2.40±1.012	2.43±1.014	2.40±1.009
ADAS-Cog 13 score, mean ± SD	21.9±6.73	22.5±6.76	22.2±7.08	22.5±6.56	22.5±6.30	22.4±6.54
ADCS-ADL-MCI score, mean ± SD	42.6±5.73	42.8±5.48	42.5±5.82	43.0±5.55	42.9±5.73	42.9±5.70

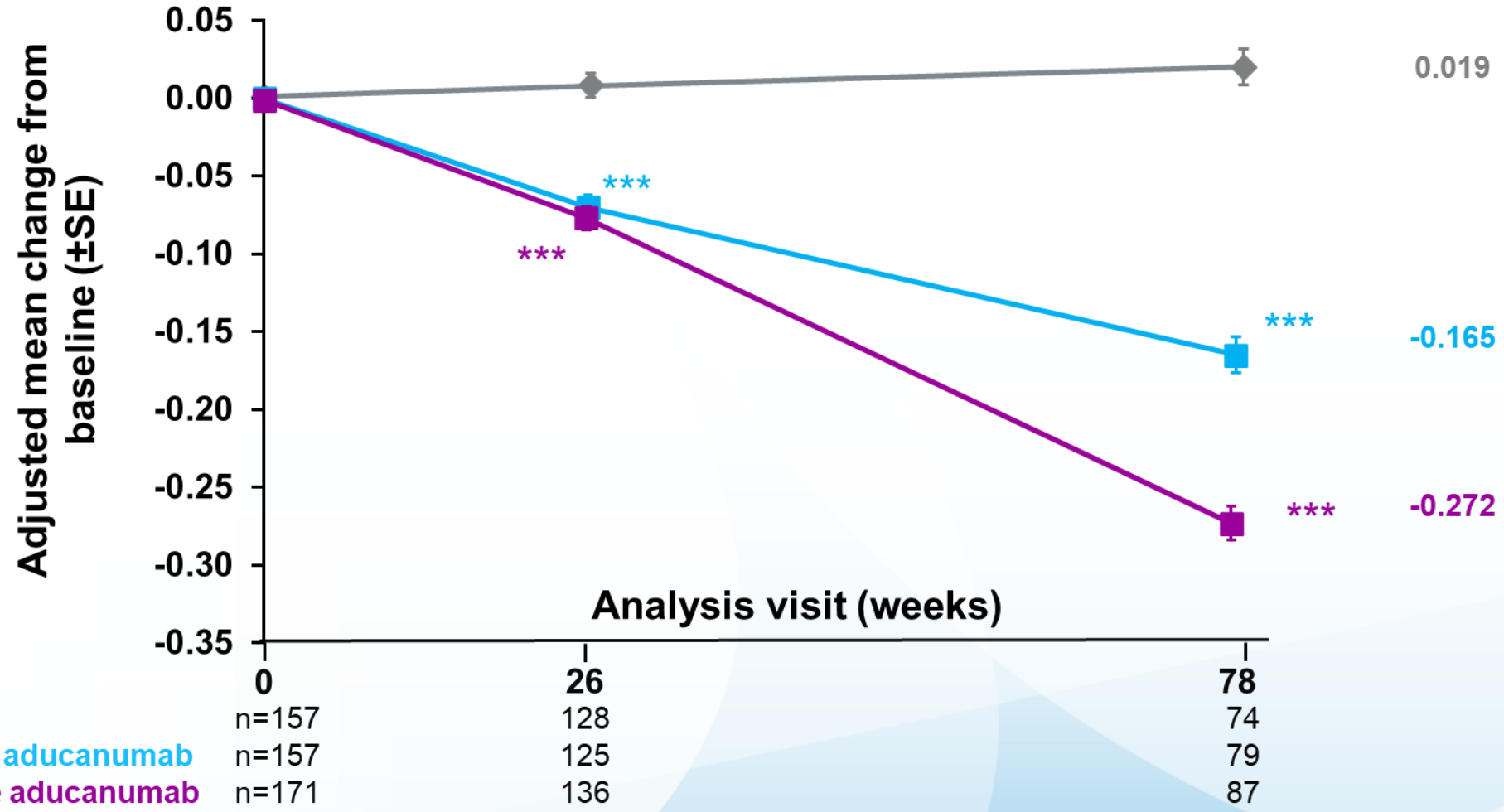
ITT population.
ADAS-Cog 13, Alzheimer's Disease Assessment Scale–Cognitive Subscale (13-item); ADCS-ADL-MCI, Alzheimer's Disease Cooperative Study–Activities of Daily Living Inventory (mild cognitive impairment version); CDR-SB, Clinical Dementia Rating–Sum of Boxes; ITT, intent to treat; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; RBANS, Repeatable Battery for Assessment of Neuropsychological Status.

EMERGE: Primary and secondary endpoints from final data set at Week 78

	Placebo decline (n=548)	Difference vs. placebo (%)[a] p-value	
		Low dose (n=543)	High dose (n=547)
CDR-SB	1.74	**-0.26** (-15%) 0.0901	**-0.39** (-22%) 0.0120
MMSE	-3.3	**-0.1** (3%) 0.7578	**0.6** (-18%) 0.0493
ADAS-Cog 13	5.162	**-0.701** (-14%) 0.1962	**-1.400** (-27%) 0.0097
ADCS-ADL-MCI	-4.3	**0.7** (-16%) 0.1515	**1.7** (-40%) 0.0006

ITT population. [a]Difference vs placebo at Week 78. Negative percentage means less progression in the treated arm. [b]Nominal for MMSE, ADAS-Cog 13, and ADCS-ADL-MCI.
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; ITT, intent to treat; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination.

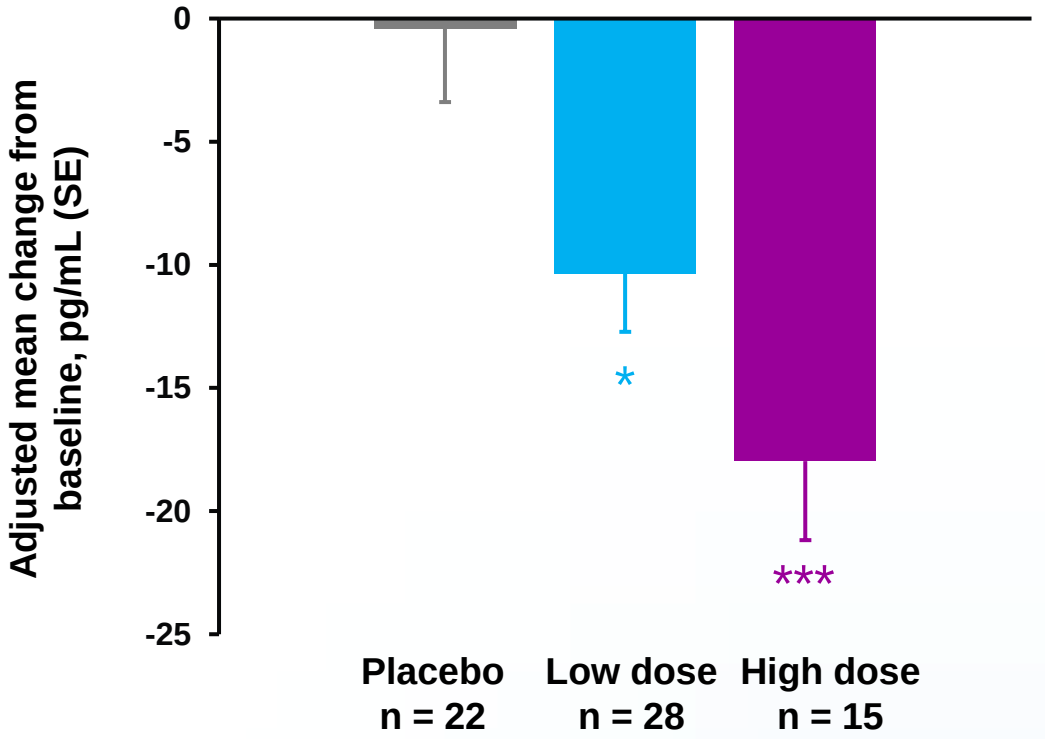
EMERGE: Longitudinal change from baseline in amyloid PET SUVR



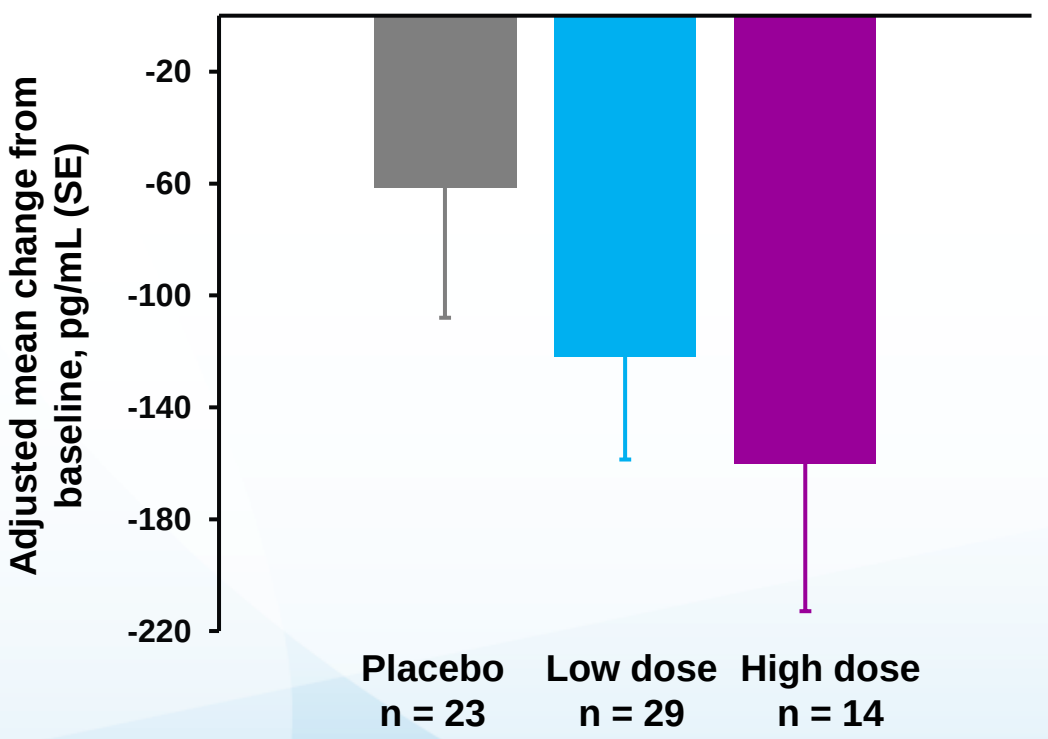
[18]F-florbetapir amyloid PET analysis population. ***p<0.0001 compared with placebo (nominal). Values at each time point were based on an MMRM model, with change from baseline in MMSE as the dependent v and with fixed effects of treatment group, categorical visit, treatment-by-visit interaction, baseline SUVR, baseline SUVR by visit interaction, baseline MMSE, Alzheimer's disease symptomatic medication use at bas region, and laboratory ApoE ε4 status. 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 tau pathology and neurodegeneration

CSF p-tau



CSF total tau



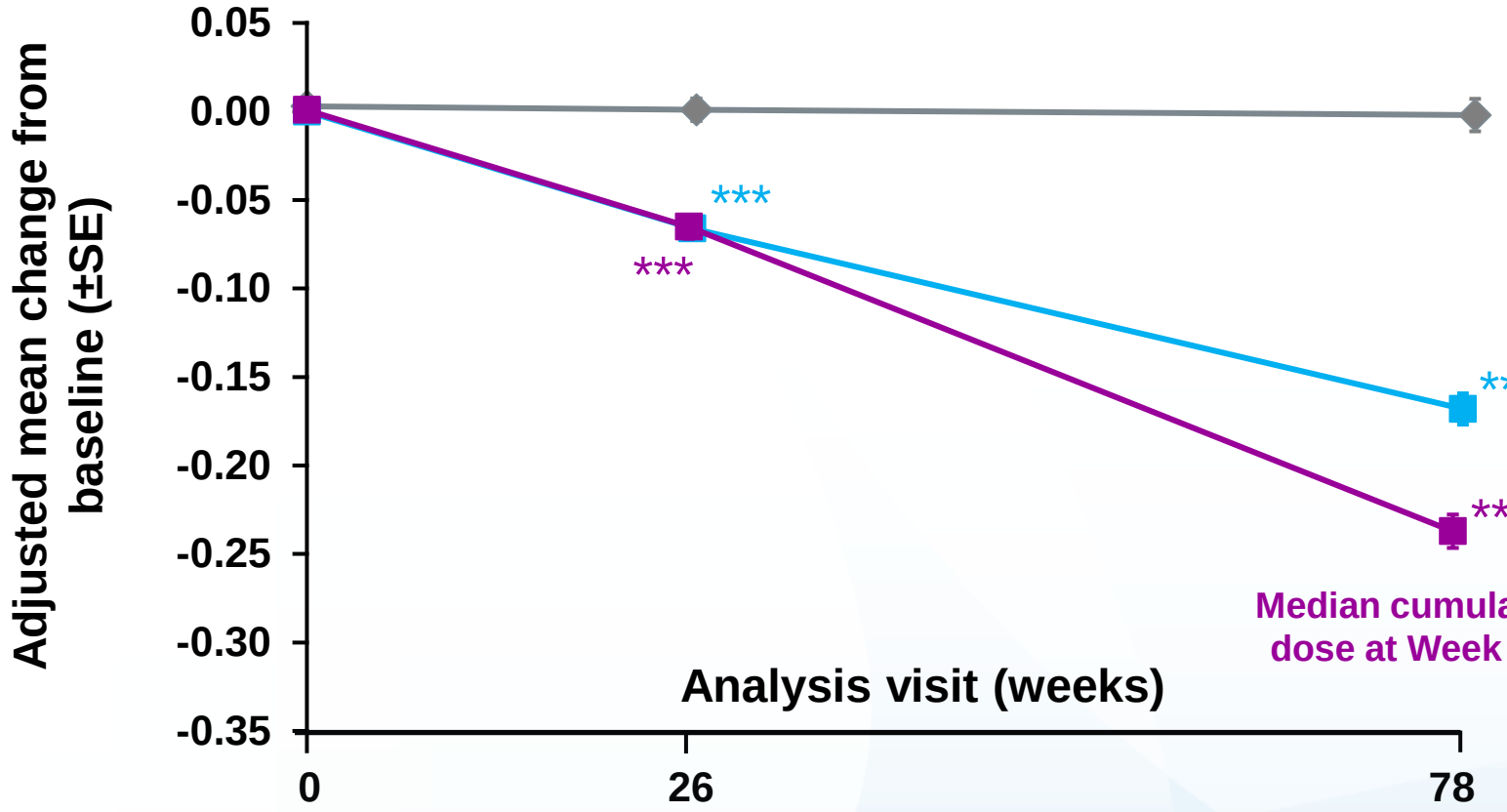
CSF modified analysis population (patients with both baseline and post-baseline CSF assessments). *p<0.05, ***p<0.001 compared with placebo (nominal). Values were based on an ANCOVA model at Week 78, with change from baseline as the dependent variable, and with categorical treatment, baseline biomarker value, baseline age, and laboratory ApoE ε4 status (carrier and non-carrier) as the independent variables.
ANCOVA, analysis of covariance; ApoE, apolipoprotein; CSF, cerebrospinal fluid; SE, standard error.

ENGAGE: Primary and secondary endpoints from final data set at Week 78

	Placebo decline (n=545)	Difference vs. placebo (%)[a] p-value[b]	
		Low dose (n=547)	High dose (n=555)
CDR-SB	1.56	**-0.18** (-12%) 0.2250	**0.03** (2%) 0.8330
MMSE	-3.5	**0.2** (-6%) 0.4795	**-0.1** (3%) 0.8106
ADAS-Cog 13	5.140	**-0.583** (-11%) 0.2536	**-0.588** (-11%) 0.2578
ADCS-ADL-MCI	-3.8	**0.7** (-18%) 0.1225	**0.7** (-18%) 0.1506

ITT population. [a]Difference vs placebo at Week 78. Negative percentage means less progression in the treated arm. [b]Nominal for MMSE, ADAS-Cog 13, and ADCS-ADL-MCI.
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; ITT, intent to treat; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination.

ENGAGE: Longitudinal change from baseline in amyloid PET SUVR

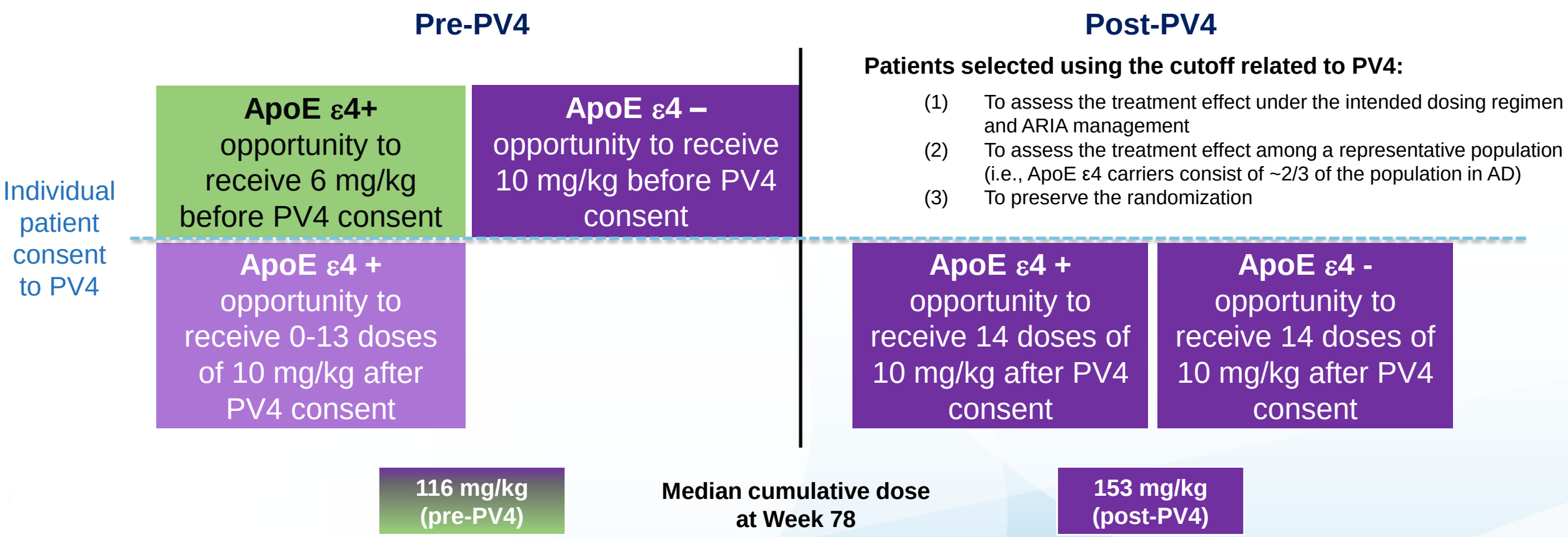


	ENGAGE	EMERGE
	-0.005	0.019
	-0.168	-0.165
	-0.238	-0.272
Median cumulative dose at Week 78[a]	126 mg/kg	140 mg/kg

Placebo	n=203	164	104
Low dose aducanumab	n=198	166	116
High dose aducanumab	n=181	149	97

[a]Calculated from patients with Week 78 PET assessment.[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 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. 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.

Defining a population by a randomized cohort who had the opportunity for all 14 doses of 10 mg/kg



ApoE, apolipoprotein E; PV4, Protocol Version 4.

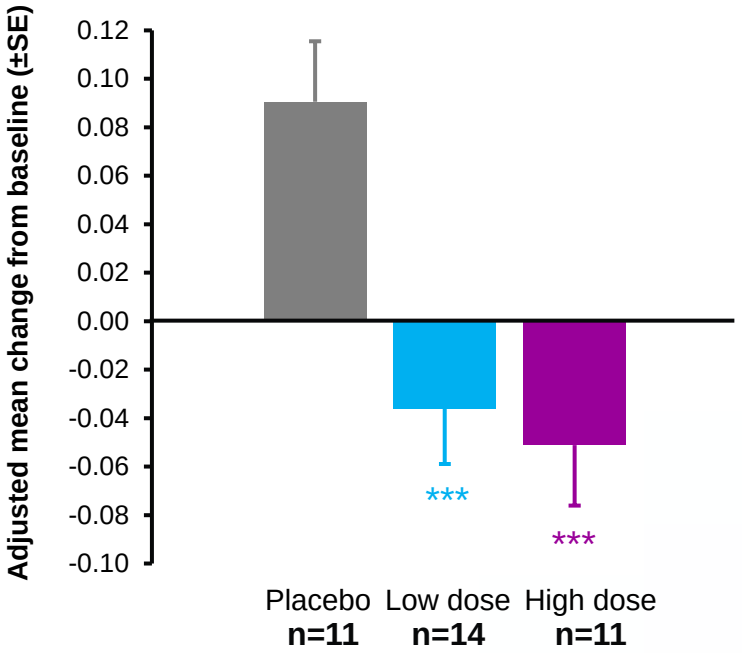
CDR-SB for ITT population compared with Post-PV4 population for EMERGE and ENGAGE at Week 78

	ITT			Post-PV4[a,b]		
EMERGE	**Placebo decline (n=548)**	**Low dose (n=543)** diff vs. placebo, (%)[c]	**High dose (n=547)** diff vs. placebo (%)[c]	**Placebo decline (n=304)**	**Low dose (n=295)** diff vs. placebo (%)[c]	**High dose (n=288)** diff vs. placebo (%)[c]
CDR-SB	1.74	**-0.26** (-15%)	**-0.39** (-22%)	1.76	**-0.42** (-24%)	**-0.53** (-30%)
ENGAGE	**Placebo decline (n=545)**	**Low dose (n=547)**	**High dose (n=555)**	**Placebo decline (n=247)**	**Low dose (n=261)**	**High dose (n=282)**
CDR-SB	1.56	**-0.18** (-12%)	**0.03** (2%)	1.79	**-0.35** (-20%)	**-0.48** (-27%)

[a]MMRM model was fitted separately for pre- and post-Protocol Version 4 set; [b]Patients who consented to PV4 or higher version prior to Week 16 in ITT population; [c]Difference vs placebo at Week 78. Negative percentage means less progression in the treated arm; N denotes the number of all randomized and dosed patients that were included in the ITT analysis.
CDR-SB, Clinical Dementia Rating–Sum of Boxes; ITT, intent to treat.

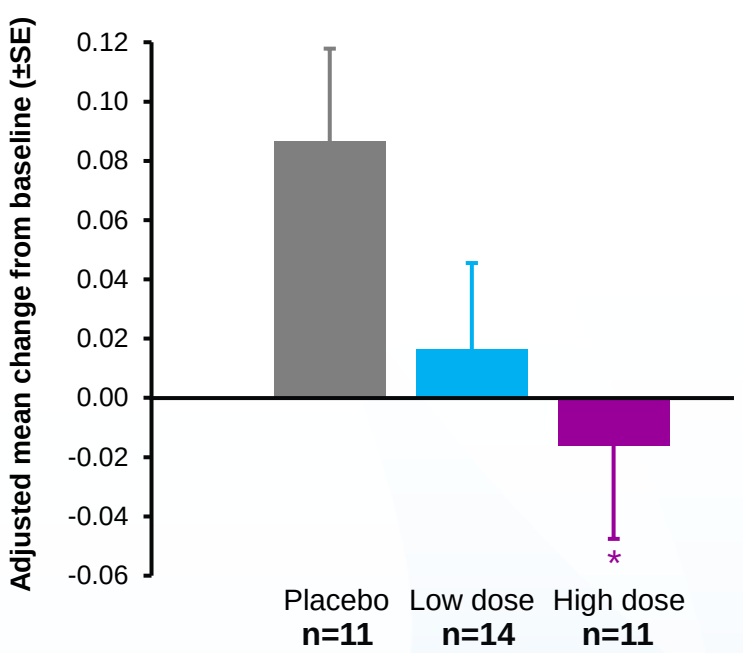
EMERGE and ENGAGE: Composite SUVR change from baseline

Medial temporal composite



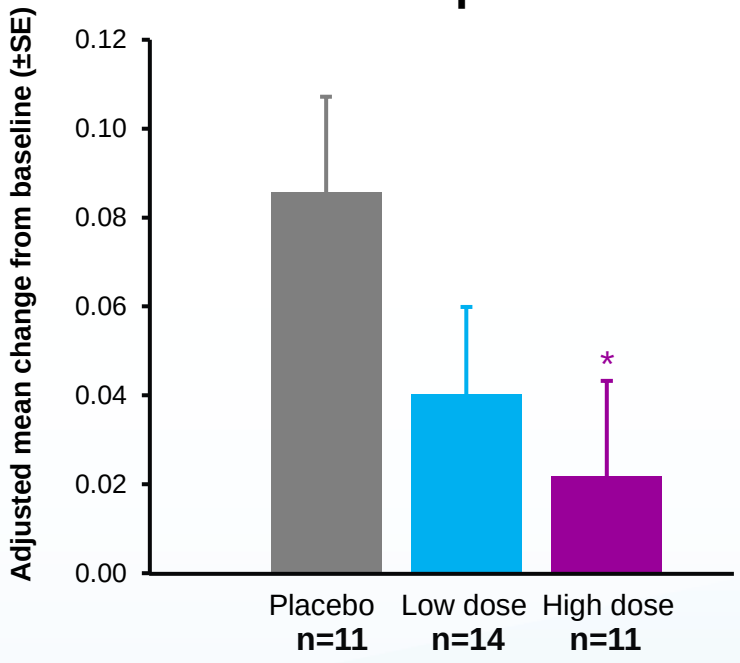
HIPPOCAMPUS
PARAHIPPOCAMPAL
TEMPORAL LOBE ANTERIOR MEDIAL
(includes Entorhinal and Amygdala)
TEMPORAL LOBE ANTERIOR LATERAL

Temporal composite



TEMPORAL LOBE Comprised of:
SUPERIOR, POSTERIOR, MIDDLE INFERIOR
POSTERIOR, SUPERIOR ANTERIOR,
FUSIFORM GYRUS

Frontal composite



FRONTAL LOBE Comprised of:
MIDDLE, PRECENTRAL, STRAIGHT GYRUS
INFERIOR, SUPERIOR
ORBITOFRONTAL CORTEX Comprised of:
ANTERIOR, MEDIAL, LATERAL, POSTERIOR

Tau PET modified analysis population (patients with both baseline and post-baseline tau PET assessments). *P <0.05, ***P<0.001 compared with placebo (nominal). Values based on an ANCOVA model, fitted wit
change from baseline as dependent variable, and with categorical treatment, baseline tau PET value and laboratory ApoE ε4 status (carrier and non-carrier) as independent variables. Due to the early termination o
studies, all the post-baseline tau PET assessments were performed within a range of 9 to 20 months post-baseline in the placebo-controlled period.
ANCOVA, analysis of covariance; PET, positron emission tomography; SUVR, standardized uptake value ratio.

EMERGE and ENGAGE: Adverse events

	EMERGE			ENGAGE		
Safety population*	Placebo (n=547)	Low dose (n=544)	High dose (n=547)	Placebo (n=541)	Low dose (n=548)	High dose (n=558)
Patients with any event, n (%)	476 (87.0)	477 (87.7)	505 (92.3)	465 (86.0)	491 (89.6)	500 (89.6)
ARIA-E	12 (2.2)	140 (25.7)	186 (34.0)	16 (3.0)	139 (25.4)	198 (35.5)
ApoE ε4 carriers	7/371 (1.9)	109/366 (29.8)	154/362 (42.5)	9/371 (2.4)	112/390 (28.7)	158/378 (41.8)
ApoE ε4 non-carriers	5/173 (2.9)	31/171 (18.1)	32/179 (17.9)	7/162 (4.3)	27/154 (17.5)	40/176 (22.7)
Headache	83 (15.2)	106 (19.5)	106 (19.4)	81 (15.0)	98 (17.9)	114 (20.4)
ARIA-H, micro-hemorrhage	38 (6.9)	88 (16.2)	102 (18.6)	31 (5.7)	85 (15.5)	98 (17.6)
Nasopharyngitis	90 (16.5)	70 (12.9)	87 (15.9)	67 (12.4)	64 (11.7)	66 (11.8)
ARIA-H, superficial siderosis	14 (2.6)	50 (9.2)	73 (13.3)	10 (1.8)	48 (8.8)	86 (15.4)
Fall	68 (12.4)	64 (11.8)	69 (12.6)	55 (10.2)	77 (14.1)	83 (14.9)
Patients permanently discontinuing treatment due to AE, n (%)	**16** (2.9)	**42** (7.7)	**48** (8.8)	**28** (5.2)	**45** (8.2)	**64** (11.5)

- Symptoms reported in patients with ARIA included: headache, dizziness, visual disturbances, nausea, and vomiting
- ARIA-E episodes generally resolved within 4–16 weeks
- The majority of patients who experienced ARIA were able to continue investigational treatment

*Patients randomized to placebo who accidentally received active dose are summarized under active groups (four in ENGAGE and one in EMERGE). All safety data presented are from the placebo-controlled period. This table includes patients who received at least one dose of investigational treatment

AE, adverse event; ARIA, amyloid-related imaging abnormality; ARIA-E, amyloid-related imaging abnormalities due to vasogenic edema; ARIA-H, amyloid-related imaging abnormalities due to micro-hemorrhages, macro-hemorrhages

Summary of aducanumab Phase 3 topline results

Following study termination based on futility, analysis of a larger dataset showed:

- In EMERGE, high dose aducanumab reduced clinical decline as measured by primary and secondary endpoints
  - In sub-studies, aducanumab showed an effect on disease related biomarkers
- In ENGAGE, aducanumab did not reduce clinical decline
  - In a post hoc analysis, data from a subset of patients with the opportunity to receive 10 mg/kg aducanumab support the positive findings of EMERGE
- The most common AEs were ARIA-E and headache
- A re-dosing study, EMBARK, is currently offering aducanumab to eligible patients who were actively enrolled in the aducanumab clinical studies

AE, adverse event; ARIA, amyloid-related imaging abnormalities; ARIA-E, amyloid-related imaging abnormalities due to vasogenic edema.