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

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**Disclosures: SBH (presenter), CvH, YT, SC, KKM, TC, SW, JL, LS, LN, RR, GD, KH, IN, YZ, CM, and AS are employees Biogen**

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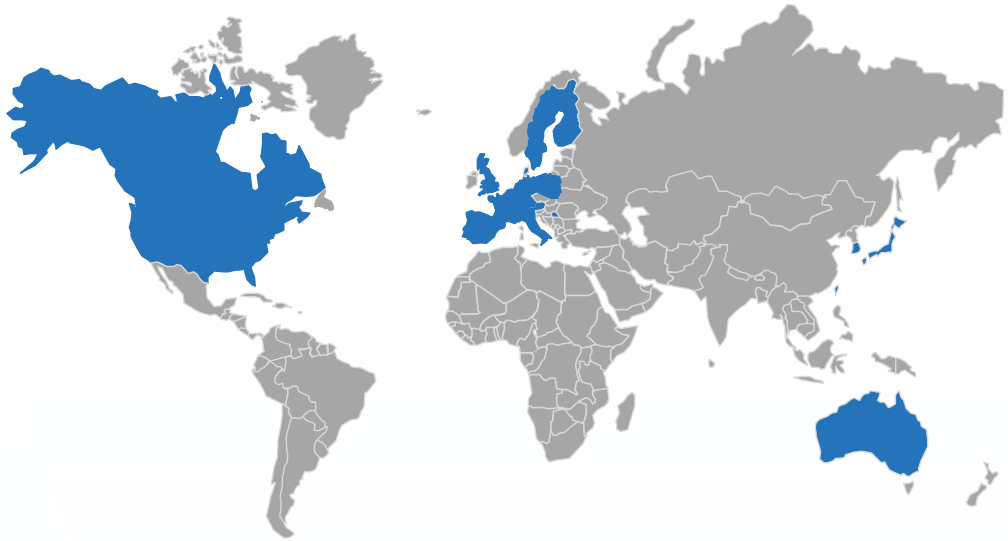
# Legal disclaimer

- 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

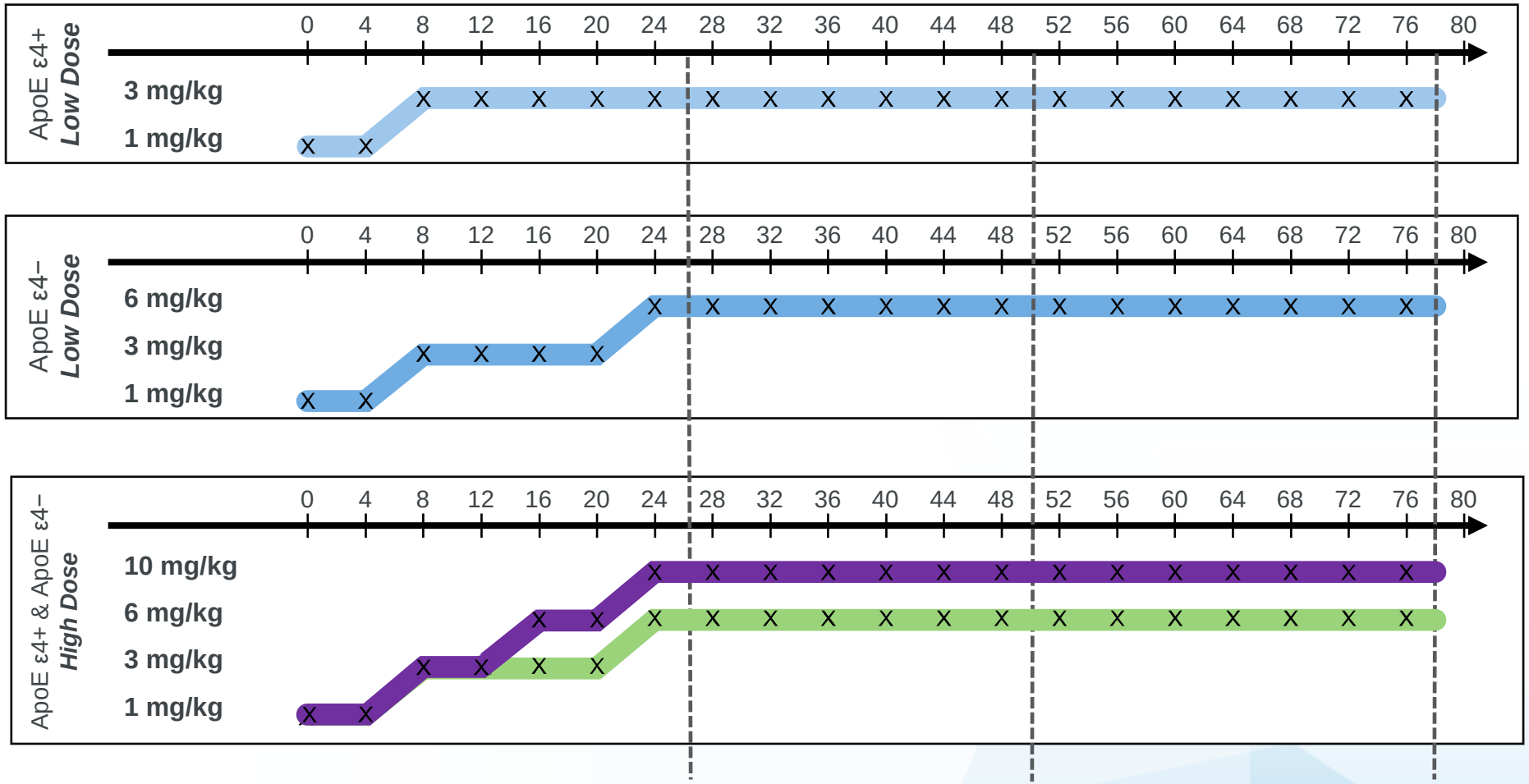
| | |
|---|---|
| **Studies** | Two 18-month, randomized, double-blind, placebo-controlled, Phase 3 studies |
| **Geography/ sample size** | 3285 patients at 348 sites in 20 countries |
| **Population** | ▪ Early Alzheimer's disease (MCI due to Alzheimer's disease + mild Alzheimer's disease dementia)<br>• 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<br>▪ 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 (%)**<br>Asian<br>White | <br>47 (8.6)<br>415 (75.7) | <br>38 (7.0)<br>418 (77.0) | <br>41 (7.5)<br>405 (74.0) | <br>55 (10.1)<br>413 (75.8) | <br>55 (10.1)<br>412 (75.3) | <br>65 (11.7)<br>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 (%)**<br>Carriers<br>Non-carriers | <br>367 (67.0)<br>178 (32.5) | <br>362 (66.7)<br>178 (32.8) | <br>365 (66.7)<br>181 (33.1) | <br>376 (69.0)<br>167 (30.6) | <br>391 (71.5)<br>156 (28.5) | <br>378 (68.1)<br>176 (31.7) |
| **Clinical stage, n (%)**<br>MCI due to Alzheimer's disease<br>Mild Alzheimer's disease | <br>446 (81.4)<br>102 (18.6) | <br>452 (83.2)<br>91 (16.8) | <br>438 (80.1)<br>109 (19.9) | <br>443 (81.3)<br>102 (18.7) | <br>440 (80.4)<br>107 (19.6) | <br>442 (79.6)<br>113 (20.4) |
| **Amyloid PET SUVR, mean composite ± SD (n)**<br>*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 (181) |

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 (%)**<br>0.5<br>1 | <br>544 (99.3)<br>3 (0.5) | <br>543 (100)<br>0 | <br>546 (99.8)<br>1 (0.2) | <br>544 (99.8)<br>1 (0.2) | <br>546 (99.8)<br>1 (0.2) | <br>554 (99.8)<br>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 |

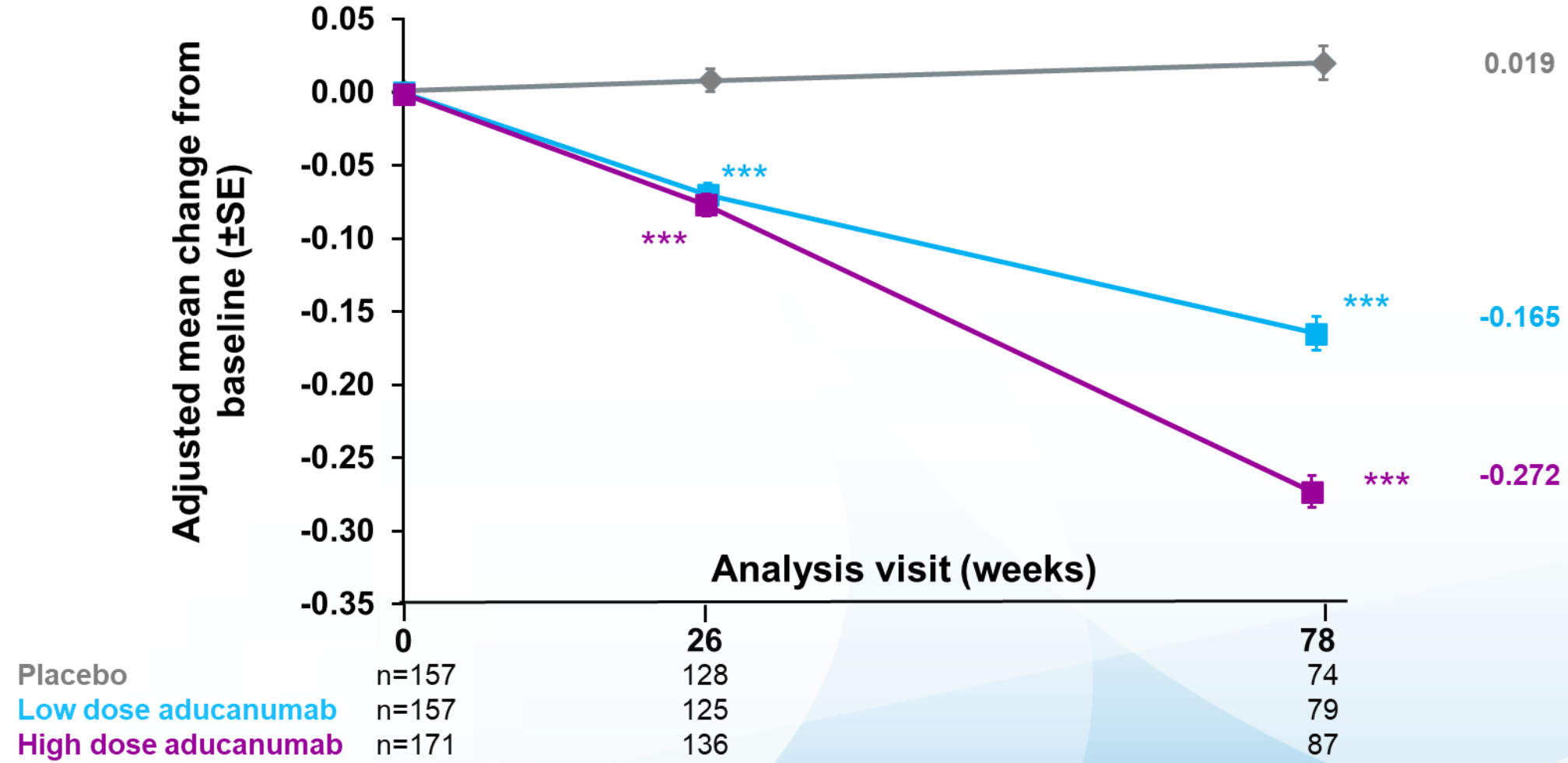
ITT population.
ADAS-Cog 13, Alzheimer's Disease Assessment Scale–Cognitive Subscale (13-item); ADCS-ADL-MCI, Alzheimer's Disease Cooperative Study–Activities of Daily Living Inventory (mild cognitive impairment version); CDR-SB, Clinical Dementia Rating–Sum of Boxes; ITT, intent to treat; MCI, mild 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%)<br>0.0901 | **-0.39** (-22%)<br>0.0120 |
| **MMSE** | -3.3 | **-0.1** (3%)<br>0.7578 | **0.6** (-18%)<br>0.0493 |
| **ADAS-Cog 13** | 5.162 | **-0.701** (-14%)<br>0.1962 | **-1.400** (-27%)<br>0.0097 |
| **ADCS-ADL-MCI** | -4.3 | **0.7** (-16%)<br>0.1515 | **1.7** (-40%)<br>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.

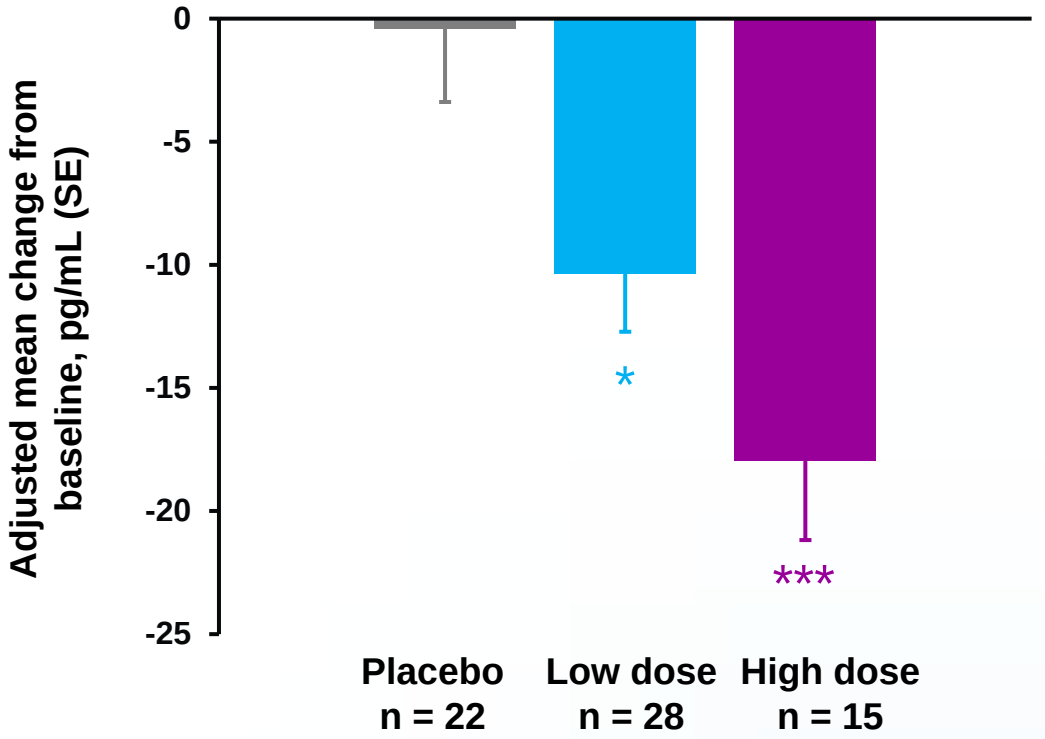
# EMERGE: Longitudinal change from baseline in amyloid PET SUVR



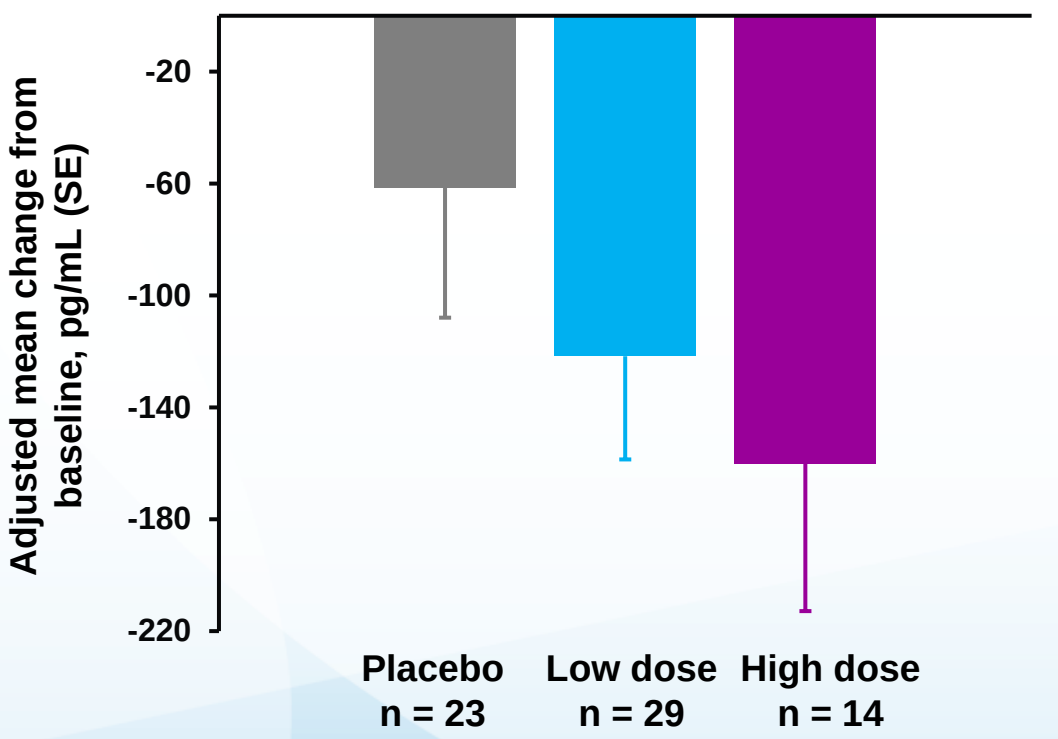

$^{18}$F-florbetapir amyloid PET analysis population. ***p<0.0001 compared with placebo (nominal). Values at each time point were based on an MMRM model, with change from baseline in MMSE as the dependent variable and with fixed effects of treatment group, categorical visit, treatment-by-visit interaction,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

# EMERGE: CSF biomarkers of tau pathology and neurodegeneration

## CSF p-tau




## CSF total tau



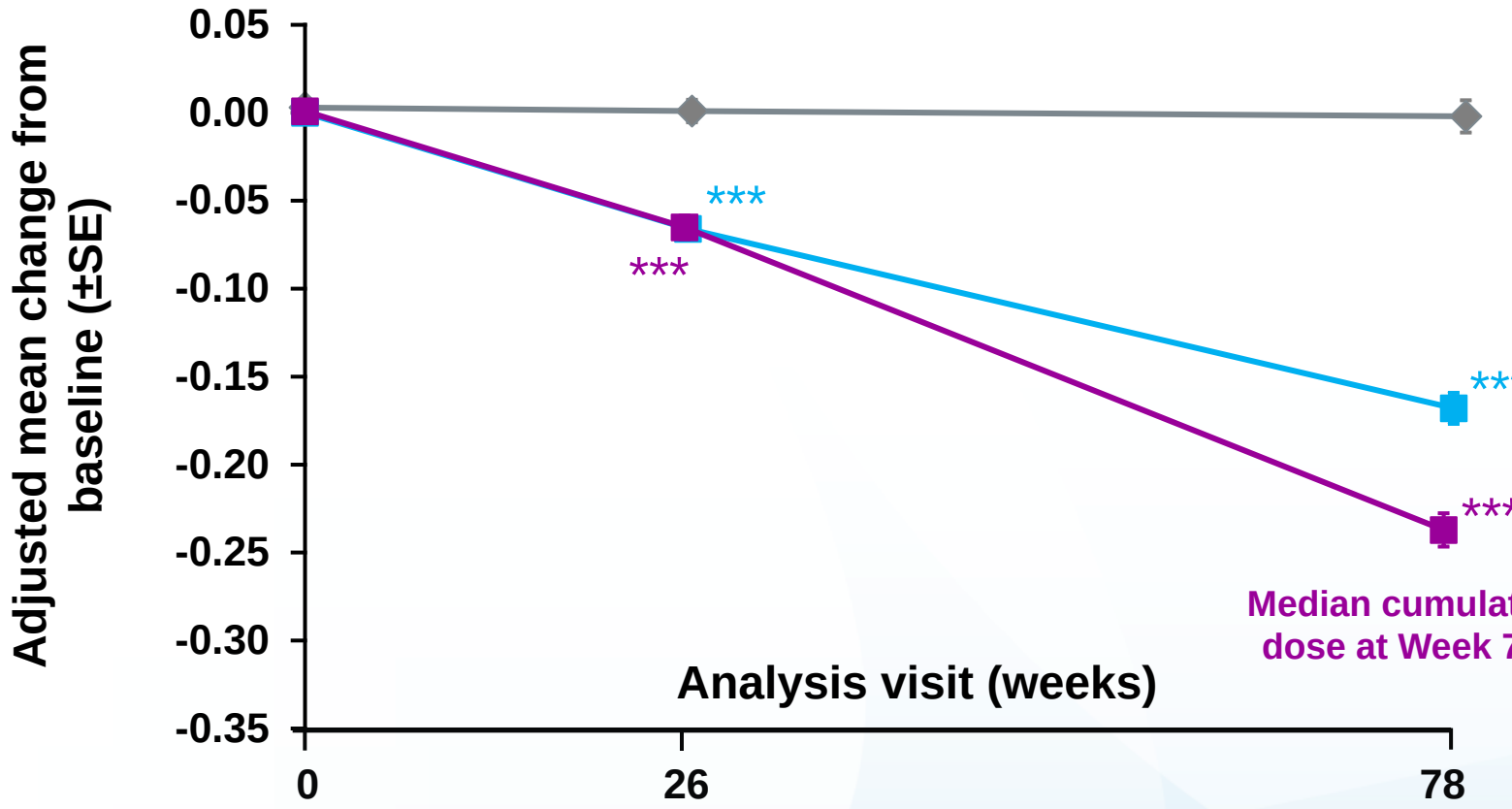

CSF modified analysis population (patients with both baseline and post-baseline CSF assessments). *p<0.05, ***p<0.001 compared with placebo (nominal). Values were based on an ANCOVA model at Week 78, fitted with change from baseline as the dependent variable, and with categorical treatment, baseline biomarker value, baseline age, and laboratory ApoE ε4 status (carrier and non-carrier) as the independent variables.
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%)<br>0.2250 | **0.03** (2%)<br>0.8330 |
| **MMSE** | -3.5 | **0.2** (-6%)<br>0.4795 | **-0.1** (3%)<br>0.8106 |
| **ADAS-Cog 13** | 5.140 | **-0.583** (-11%)<br>0.2536 | **-0.588** (-11%)<br>0.2578 |
| **ADCS-ADL-MCI** | -3.8 | **0.7** (-18%)<br>0.1225 | **0.7** (-18%)<br>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

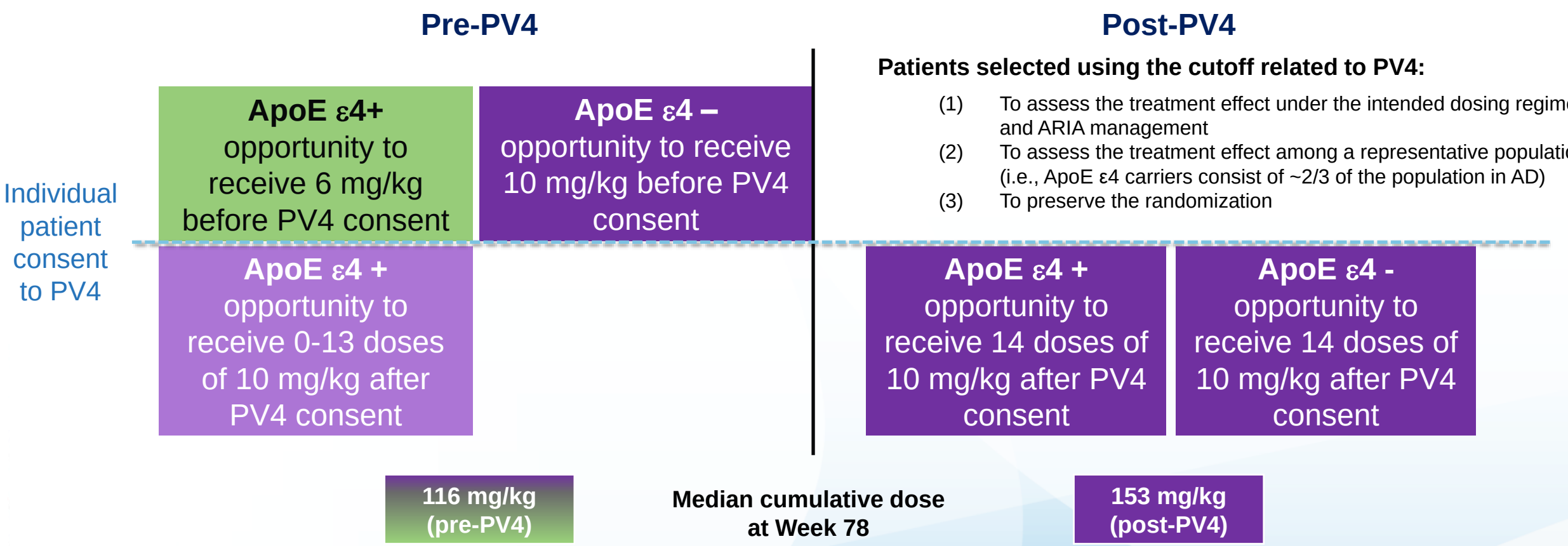



| | ENGAGE | EMERGE |
|---|---|---|
| Placebo | -0.005 | 0.019 |
| Low dose aducanumab | -0.168 | -0.165 |
| High dose aducanumab | -0.238 | -0.272 |
| Median cumulative dose at Week 78[a] | 126 mg/kg | 140 mg/kg |

| | | | |
|---|---|---|---|
| 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, 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. 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.

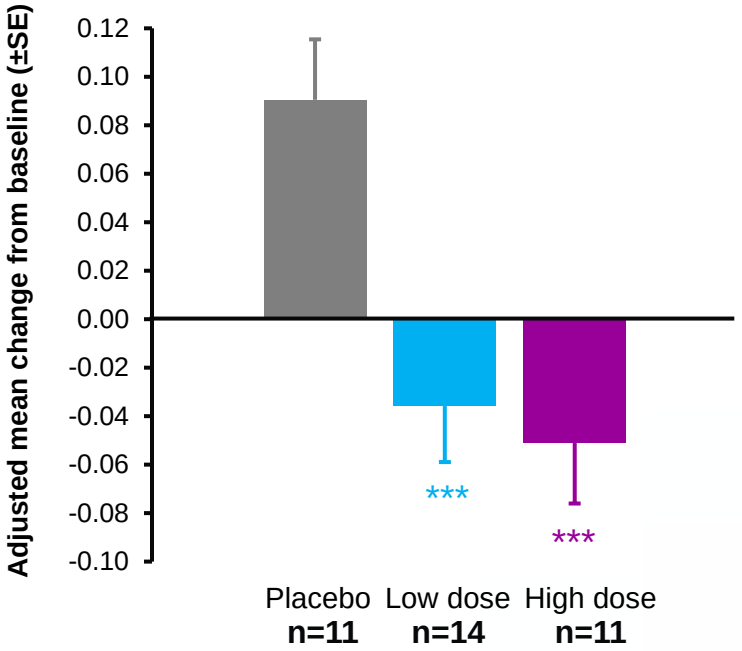
# CDR-SB for ITT population compared with Post-PV4 population for EMERGE and ENGAGE at Week 78

| | 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.

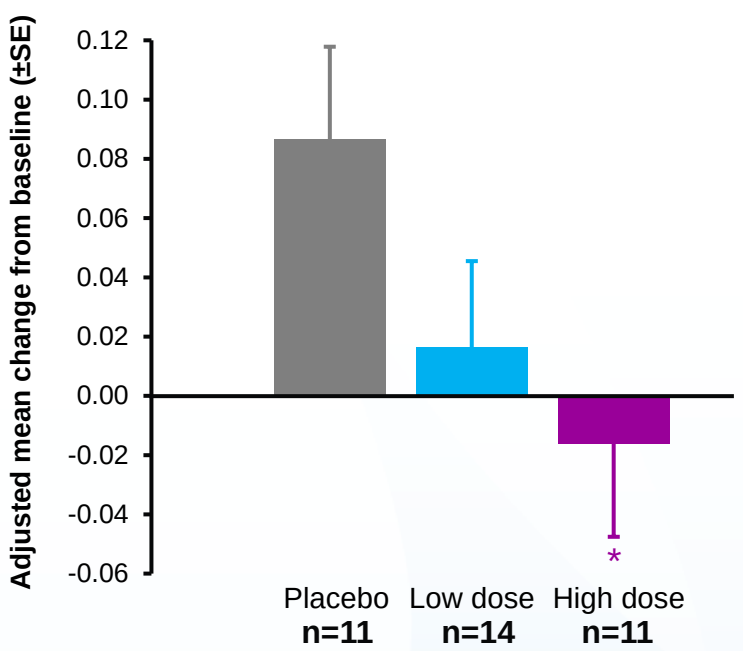
# EMERGE and ENGAGE: Composite SUVR change from baseline

## Medial temporal composite



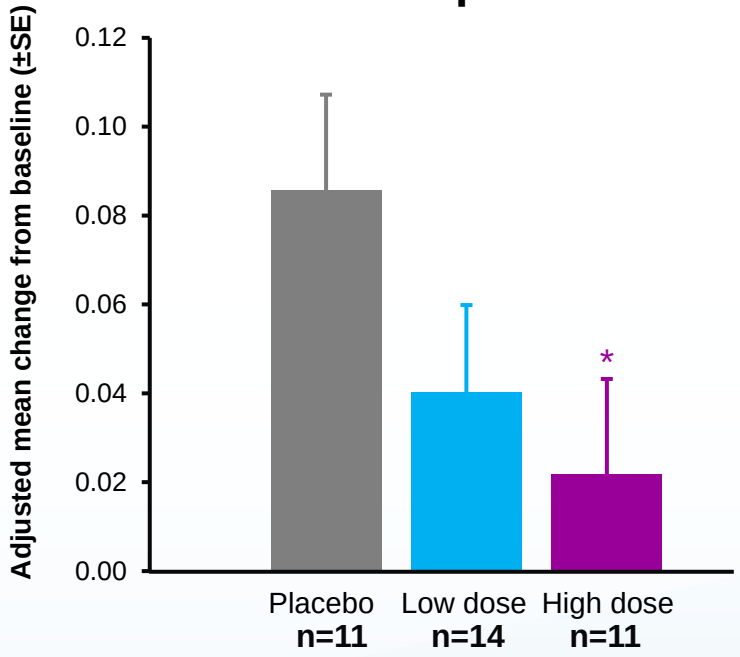

HIPPOCAMPUS
PARAHIPPOCAMPAL
TEMPORAL LOBE ANTERIOR MEDIAL
(includes Entorhinal and Amygdala)
TEMPORAL LOBE ANTERIOR LATERAL

## 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 with 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 of the 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

| Safety population* | EMERGE | | | ENGAGE | | |
|---|---|---|---|---|---|---|
| | 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.