

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

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# 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; the impact related to the effect of COVID-19 or other public health epidemics on our operations, including employees; 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.

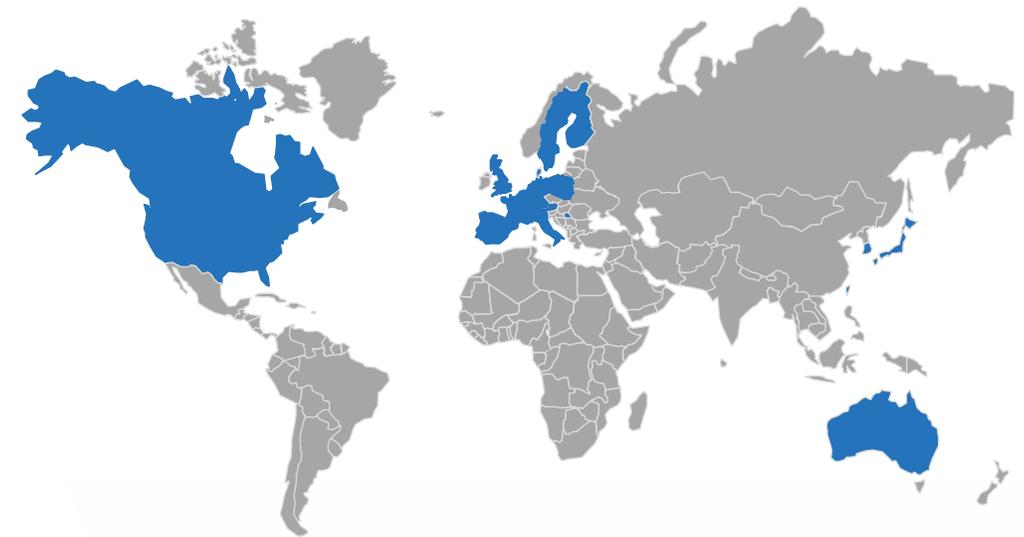


# Legal disclaimer

- 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

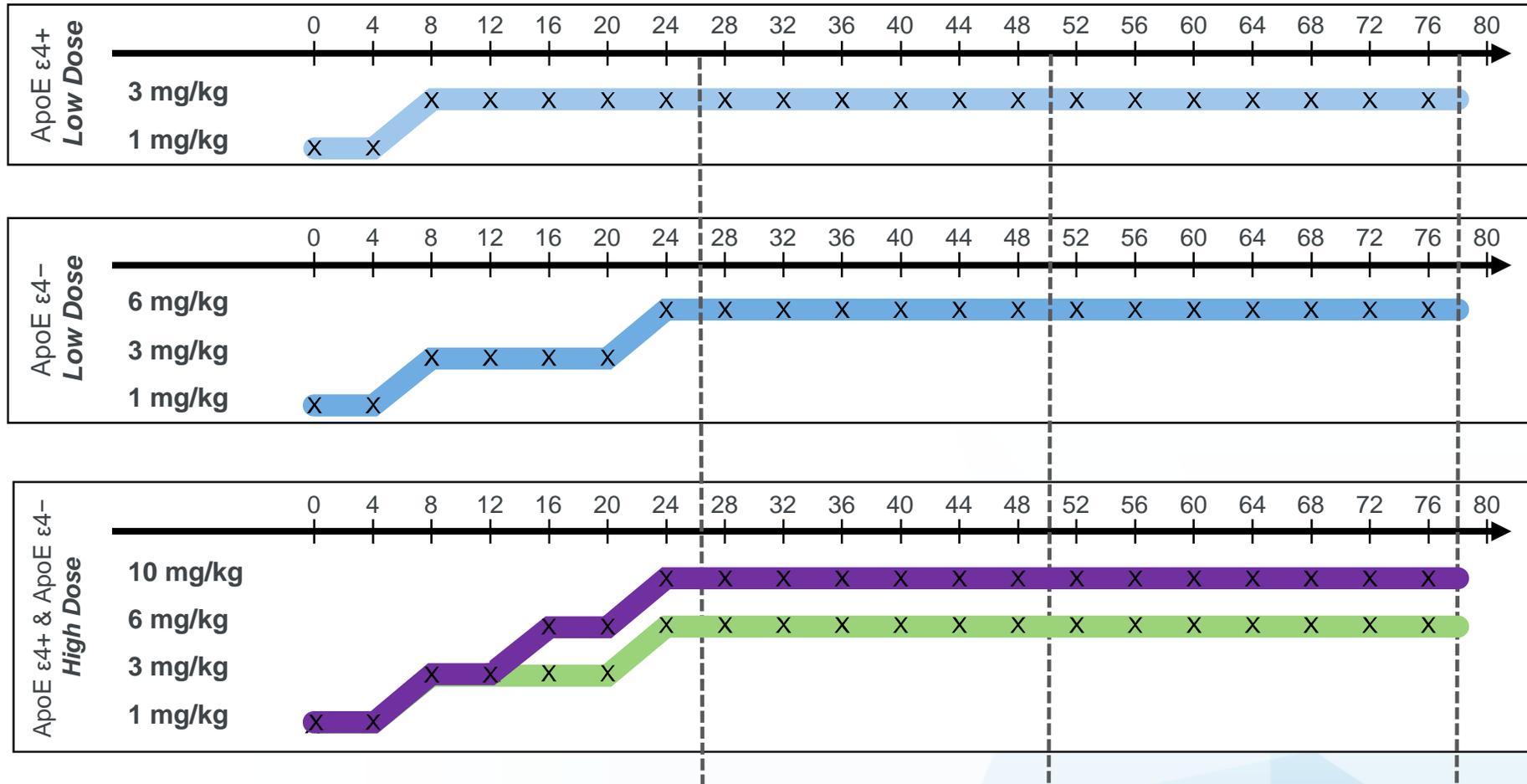
# Aducanumab Phase 3 studies EMERGE and ENGAGE

<b>Studies</b>	Two 18-month, randomized, double-blind, placebo-controlled, Phase 3 studies
<b>Geography/ sample size</b>	3285 patients at 348 sites in 20 countries
<b>Population</b>	<ul style="list-style-type: none"> <li>▪ Early Alzheimer's disease (MCI due to Alzheimer's disease + mild Alzheimer's disease dementia)             <ul style="list-style-type: none"> <li>• MMSE 24-30, CDR-G 0.5, RBANS ≤ 85, with confirmed amyloid pathology</li> </ul> </li> </ul>
<b>Doses</b>	<ul style="list-style-type: none"> <li>▪ Two dosing regimens (low and high) and placebo; randomized 1:1:1</li> </ul>
<b>Primary endpoint</b>	<ul style="list-style-type: none"> <li>▪ CDR-SB at 18 months</li> </ul>
<b>Other endpoints</b>	<ul style="list-style-type: none"> <li>▪ Secondary: MMSE, ADAS-Cog 13, ADCS-ADL-MCI</li> <li>▪ Sub-studies: amyloid PET, tau PET, CSF disease-related biomarkers</li> </ul>



**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

# EMERGE and ENGAGE: Dose regimen

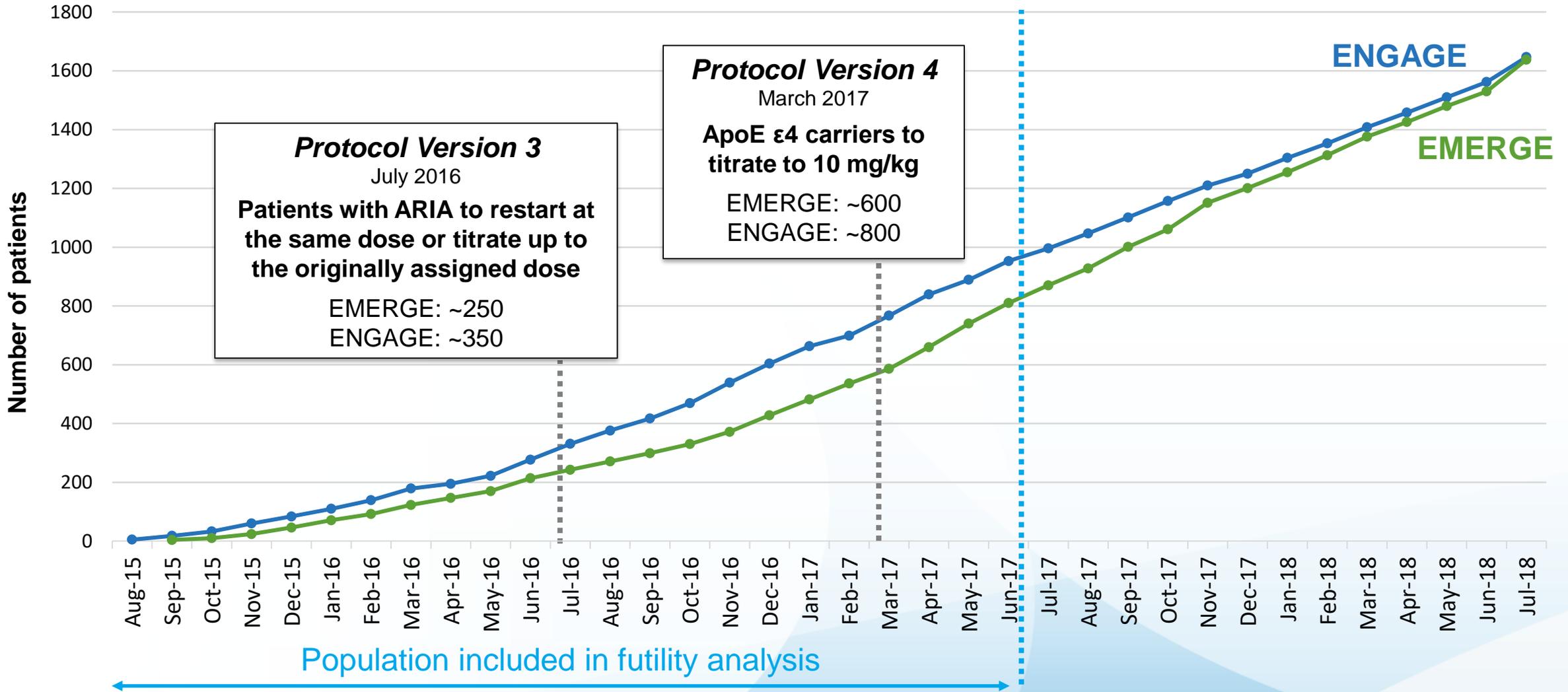


- Low dose titrated to 3 or 6 mg/kg
- Maintained throughout study

- 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*

# Enrollment and timing of key protocol amendments



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

# EMERGE and ENGAGE Topline Results

# EMERGE and ENGAGE: Data sets

Data set	Population	EMERGE n (%)	ENGAGE n (%)
<b>Futility</b>	<b>Opportunity to complete (OTC)</b> Patients who have had the opportunity to complete Week 78 visit by December 26, 2018	803 (49%)	945 (57%)
<b>Larger data set<sup>a</sup></b>	<b>Opportunity to complete (OTC)</b> Patients who have had the opportunity to complete Week 78 visit by March 20, 2019	982 (60%)	1084 (66%)
	<b>Intent to treat (ITT)</b> All patient data (data after March 20 are censored for efficacy analyses) <i>Data cleaning was ongoing for a small amount of data</i>	1638 (100%)	1647 (100%)
<b>Final data set</b>	<b>Intent to treat (ITT)</b> All patient data (data after March 20 are censored for efficacy analyses)	1638 (100%)	1647 (100%)
<b>Sub-studies</b>	<b>Amyloid PET</b>	485 (30%)	582 (35%)
	<b>CSF</b>	68 (4%)	57 (3%)
	<b>Tau PET</b>	6 (<1%)	30 (2%)

<sup>a</sup>Unless otherwise specified, all of the results presented in this presentation are based on the larger dataset.  
CSF, cerebrospinal fluid; ITT, intent to treat; OTC, opportunity to complete; PET, positron emission tomography.

# EMERGE and ENGAGE

Futility analysis

# EMERGE and ENGAGE: Prespecified futility analysis

- **Conditional power:** probability that primary efficacy endpoint analysis would be statistically significant at final analysis
- **Prespecified criteria:** both dose arms of both studies having less than 20% conditional power to meet the primary endpoint at final analysis
- **Prespecified methodology:** given identical study design, conditional power would be calculated using pooled data from both studies to predict the future behavior of the remaining patients
  - Pooling was believed to be a more powerful statistical methodology
- Using this methodology, the futility criteria were met
- At the time of futility analysis, EMERGE was trending positive, whereas ENGAGE was not

# Phase 3 Topline Results

EMERGE

# EMERGE: Baseline demographics

	EMERGE		
	Placebo (n=548)	Low dose (n=543)	High dose (n=547)
<b>Age in years, mean ± SD</b>	70.8±7.40	70.6±7.45	70.6±7.47
<b>Female, n (%)</b>	290 (52.9)	269 (49.5)	284 (51.9)
<b>Race, n (%)</b>			
Asian	47 (8.6)	38 (7.0)	41 (7.5)
White	415 (75.7)	418 (77.0)	405 (74.0)
<b>Education years, mean ± SD</b>	14.5±3.82	14.5±3.63	14.6±3.74
<b>Alzheimer's disease medications used, n (%)</b>	279 (50.9)	277 (51.0)	277 (50.6)
<b>ApoE ε4, n (%)</b>			
Carriers	367 (67.0)	362 (66.7)	365 (66.7)
Non-carriers	178 (32.5)	178 (32.8)	181 (33.1)
<b>Clinical stage, n (%)</b>			
MCI due to Alzheimer's disease	446 (81.4)	452 (83.2)	438 (80.1)
Mild Alzheimer's disease	102 (18.6)	91 (16.8)	109 (19.9)
<b>Amyloid PET SUVR, mean composite ± SD (n)</b> <i>PET sub-study population only</i>	1.37±0.175 (157)	1.39±0.181 (157)	1.38±0.183 (171)

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.

# EMERGE: Baseline disease characteristics

	EMERGE		
	Placebo (n=548)	Low dose (n=543)	High dose (n=547)
<b>RBANS delayed memory score, mean ± SD</b>	60.5±14.23	60.0±14.02	60.7±14.15
<b>MMSE score, mean ± SD</b>	26.4±1.78	26.3±1.72	26.3±1.68
<b>CDR global score, n (%)</b>			
0.5	544 (99.3)	543 (100)	546 (99.8)
1	3 (0.5)	0	1 (0.2)
<b>CDR-SB score, mean ± SD</b>	2.47±0.999	2.46±1.011	2.51±1.053
<b>ADAS-Cog 13 score, mean ± SD</b>	21.9±6.73	22.5±6.76	22.2±7.08
<b>ADCS-ADL-MCI score, mean ± SD</b>	42.6±5.73	42.8±5.48	42.5±5.82

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: Patient disposition

Randomized	EMERGE (N=1643)		
Dosed	n=1638		
	Placebo n=548	Low dose n=543	High dose n=547
<b>Discontinued treatment<sup>a</sup>, n (%)</b>	<b>82 (15.0)</b>	<b>108 (19.9)</b>	<b>131 (23.9)</b>
Adverse event	16 (2.9)	41 (7.6)	46 (8.4)
Consent withdrawn	6 (1.1)	22 (4.1)	18 (3.3)
Death	5 (0.9)	0	5 (0.9)
Study visit burden	2 (0.4)	7 (1.3)	5 (0.9)
Site terminated by sponsor	21 (3.8)	10 (1.8)	14 (2.6)
Other	23 (4.2)	23 (4.2)	28 (5.1)
<b>Withdrew from study<sup>a</sup>, n (%)</b>	<b>39 (7.1)</b>	<b>54 (9.9)</b>	<b>66 (12.1)</b>
Adverse event	10 (1.8)	11 (2.0)	18 (3.3)
Consent withdrawn	8 (1.5)	28 (5.2)	22 (4.0)
Death	5 (0.9)	0	6 (1.1)
Study visit burden	2 (0.4)	7 (1.3)	5 (0.9)
Site terminated by sponsor	0	0	1 (0.2)
Other	3 (0.5)	4 (0.7)	3 (0.5)
<b>Completed placebo-controlled period, n (%)</b>	<b>275 (50.2)</b>	<b>274 (50.5)</b>	<b>285 (52.1)</b>

ITT population. <sup>a</sup>Some categories with less than 1% patients are not displayed, including lost to follow-up, disease progression, pregnancy, investigator decision, relocation, change of treatment, withdrawal by parent/guardian, protocol amendment, site terminated by investigator and loss of capacity. ITT, intent to treat.

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

	Placebo decline (n=548)	Difference vs. placebo (%) <sup>a</sup> p-value <sup>b</sup>	
		Low dose (n=543)	High dose (n=547)
<b>CDR-SB</b>	1.74	<b>-0.25</b> (-14%) 0.1171	<b>-0.40</b> (-23%) 0.0101
<b>MMSE</b>	-3.3	<b>-0.1</b> (3%) 0.6900	<b>0.5</b> (-15%) 0.0620
<b>ADAS-Cog 13</b>	5.171	<b>-0.747</b> (-14%) 0.1672	<b>-1.395</b> (-27%) 0.0098
<b>ADCS-ADL-MCI</b>	-4.3	<b>0.7</b> (-16%) 0.1556	<b>1.7</b> (-40%) 0.0009

ITT population. <sup>a</sup>Difference vs placebo at Week 78. Negative percentage means less progression in the treated arm. <sup>b</sup>Nominal.

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.

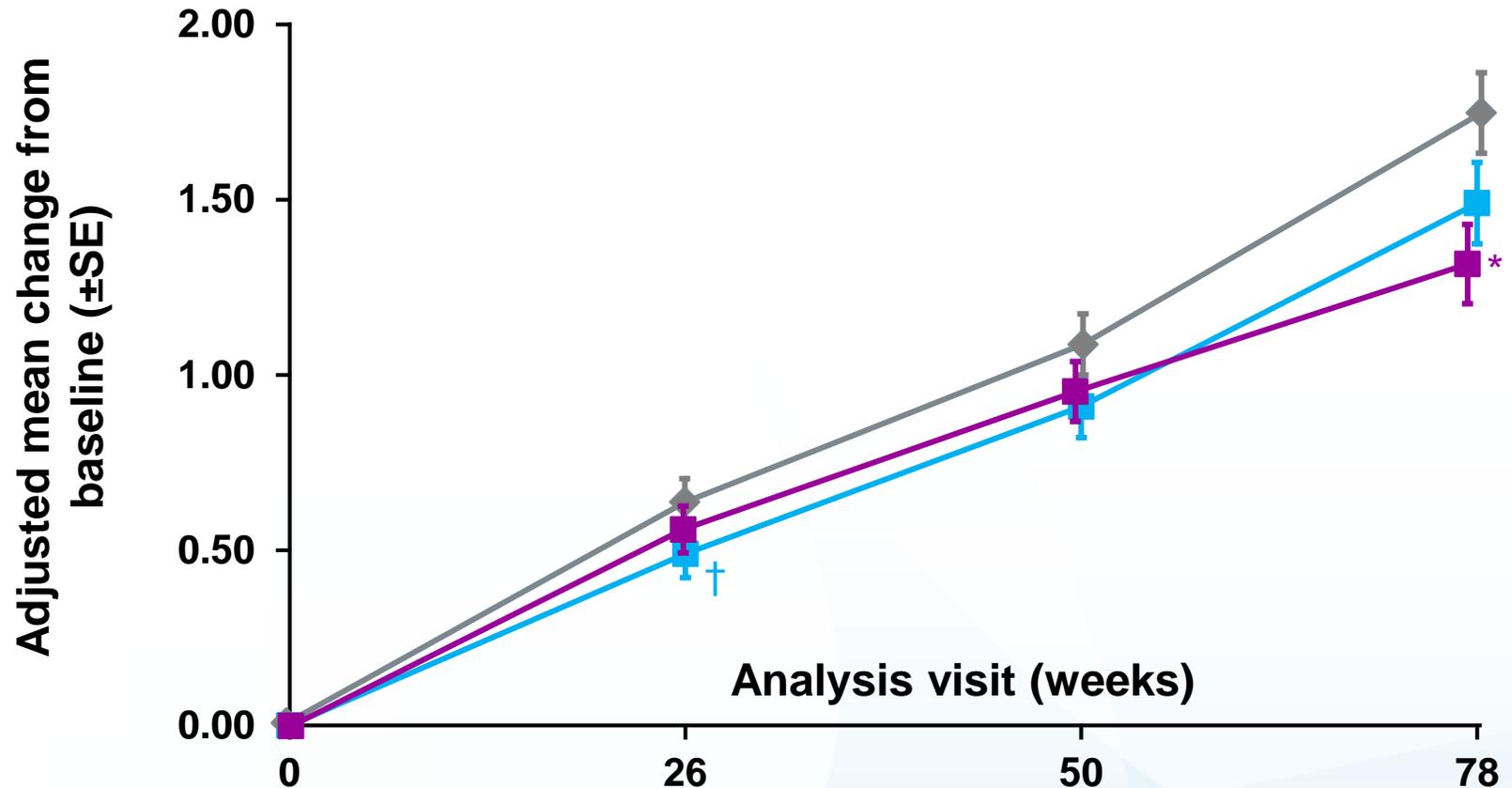
# EMERGE: Primary and secondary endpoints from final data set at Week 78

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

ITT population. <sup>a</sup>Difference vs placebo at Week 78. Negative percentage means less progression in the treated arm.

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.

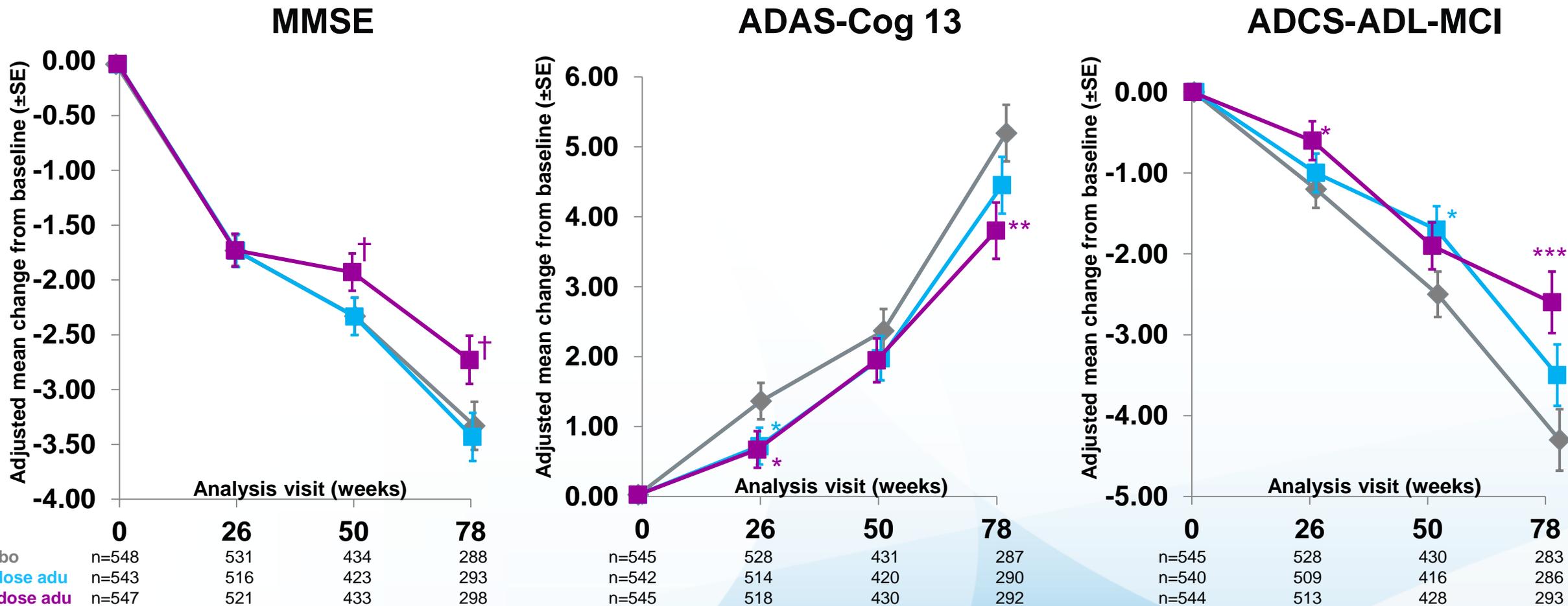
# EMERGE: Longitudinal change from baseline in CDR-SB



Placebo	n=547	531	429	288
Low dose aducanumab	n=543	512	420	289
High dose aducanumab	n=547	513	431	299

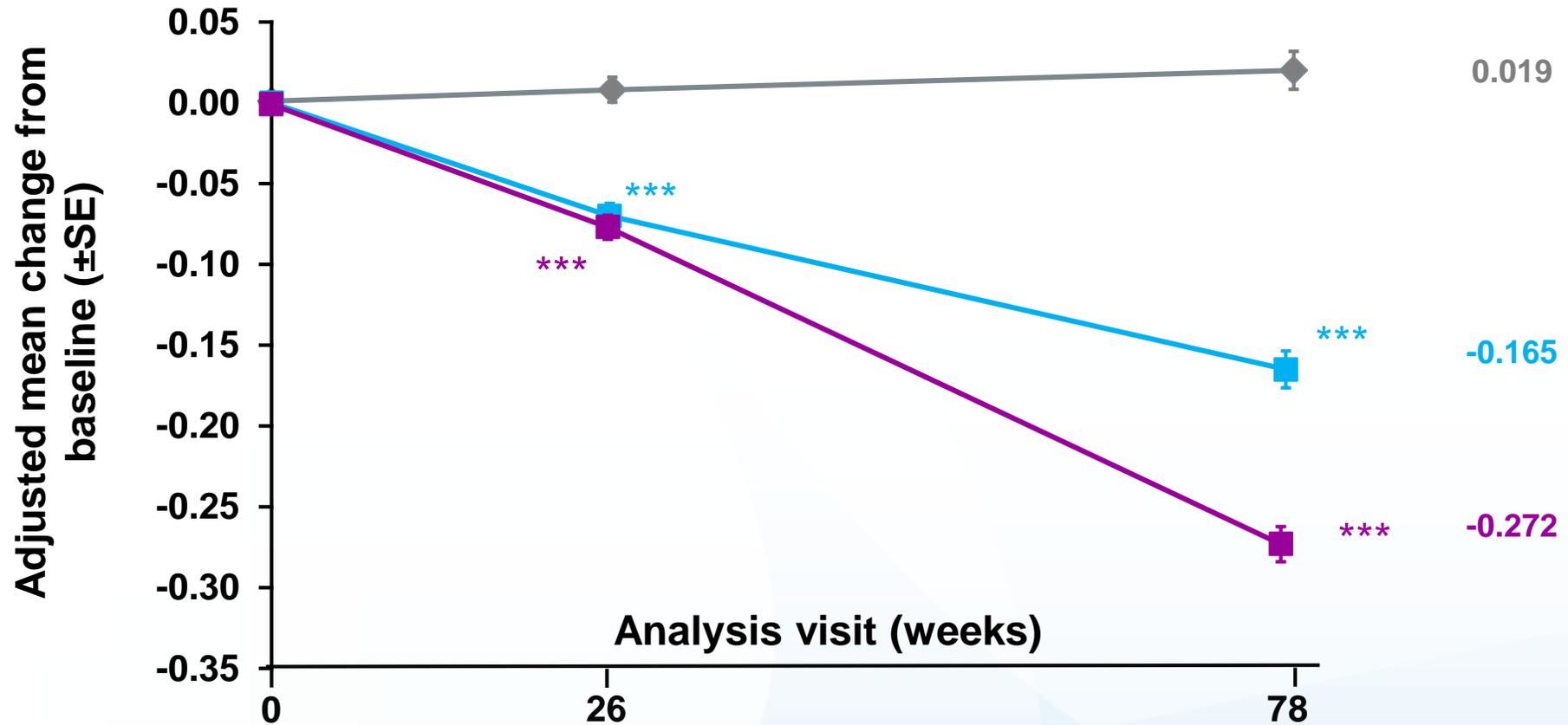
ITT population. \*p <0.05, †p <0.1 and ≥0.05 compared with placebo (nominal). Values at each time point were based on an MMRM model, with change from baseline in CDR-SB as the dependent variable and with fixed effects of treatment group, categorical visit, treatment-by-visit interaction, baseline CDR-SB, 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; ITT, intent to treat; MMRM, mixed model for repeated measure; MMSE, Mini Mental State Examination; SE, standard error.

# EMERGE: Longitudinal change from baseline in MMSE, ADAS-Cog 13 and ADCS-ADL-MCI



ITT population. †p<0.1 and ≥0.05, \*p<0.05, \*\*p<0.01, \*\*\*p<0.001 compared with placebo (nominal). Values at each time point were based on an MMRM model, with change from baseline in MMSE, ADAS-Cog 13, or ADCS-ADL-MCI as the dependent variable and with fixed effects of treatment group, categorical visit, treatment-by-visit interaction, baseline measure, baseline measure by visit interaction, Alzheimer's disease symptomatic medication use at baseline, region, and laboratory ApoE ε4 status. 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); ApoE, apolipoprotein E; ITT, intent to treat; MMRM, mixed model for repeated measure; MMSE, Mini Mental State Examination; SE, standard error.

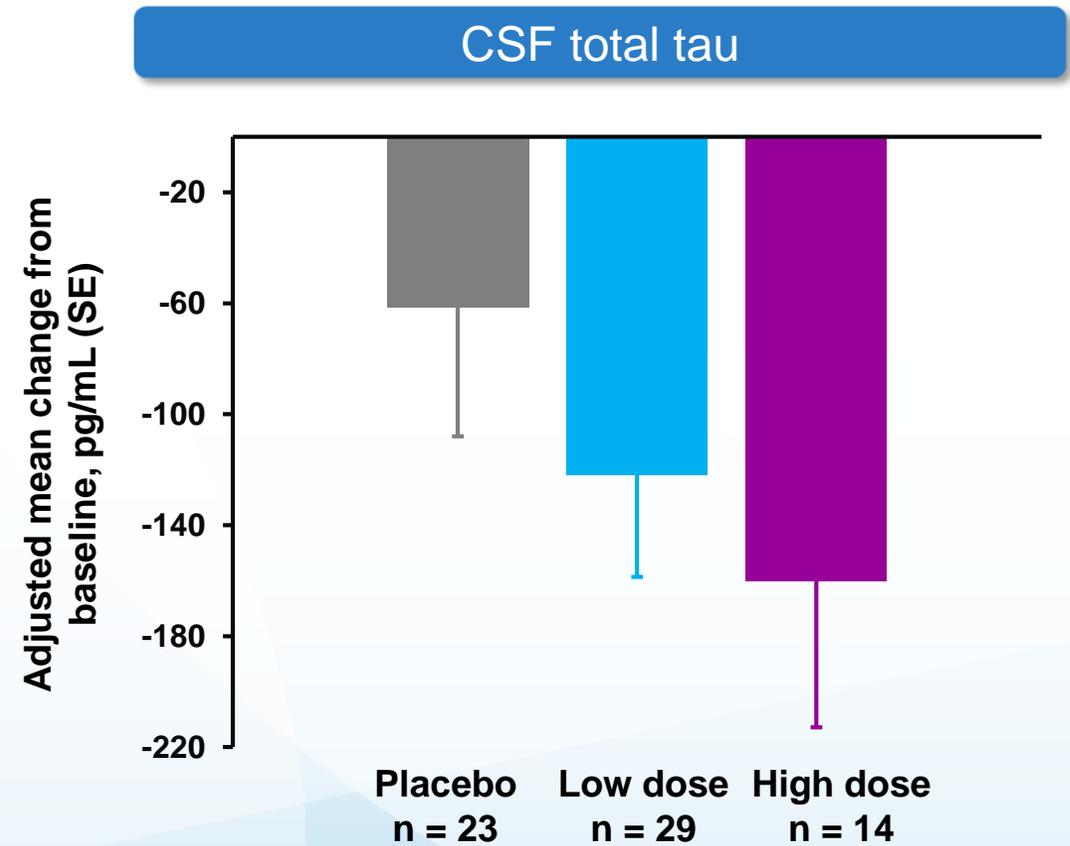
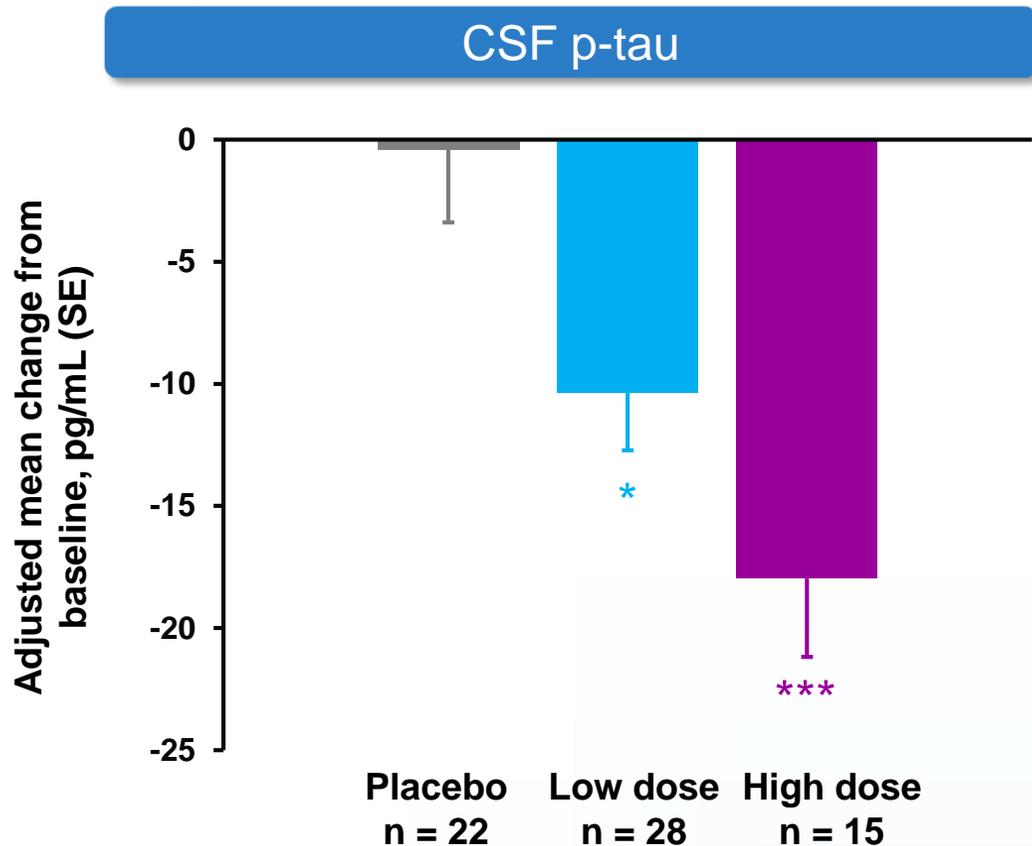
# EMERGE: Longitudinal change from baseline in amyloid PET SUVR



Placebo	n=157	128	74
Low dose aducanumab	n=157	125	79
High dose aducanumab	n=171	136	87

<sup>18</sup>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



# Phase 3 Topline Results

ENGAGE

# ENGAGE: Baseline demographics

	ENGAGE		
	Placebo (n=545)	Low dose (n=547)	High dose (n=555)
<b>Age in years, mean ± SD</b>	69.8±7.72	70.4±6.96	70.0±7.65
<b>Female, n (%)</b>	287 (52.7)	284 (51.9)	292 (52.6)
<b>Race, n (%)</b>			
Asian	55 (10.1)	55 (10.1)	65 (11.7)
White	413 (75.8)	412 (75.3)	413 (74.4)
<b>Education years, mean ± SD</b>	14.7±3.66	14.6±3.77	14.6±3.72
<b>Alzheimer's disease medications used, n (%)</b>	293 (53.8)	307 (56.1)	307 (55.3)
<b>ApoE ε4, n (%)</b>			
Carriers	376 (69.0)	391 (71.5)	378 (68.1)
Non-carriers	167 (30.6)	156 (28.5)	176 (31.7)
<b>Clinical stage, n (%)</b>			
MCI due to Alzheimer's disease	443 (81.3)	440 (80.4)	442 (79.6)
Mild Alzheimer's disease	102 (18.7)	107 (19.6)	113 (20.4)
<b>Amyloid PET SUVR, mean composite ± SD (n)</b> <i>PET sub-study population only</i>	1.38±0.198 (203)	1.39±0.186 (198)	1.41±0.177 (181)

ITT population.

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

# ENGAGE: Baseline disease characteristics

	ENGAGE		
	Placebo (n=545)	Low dose (n=547)	High dose (n=555)
<b>RBANS delayed memory score, mean ± SD</b>	60.0±13.65	59.5±14.16	60.6±14.09
<b>MMSE score, mean ± SD</b>	26.4±1.73	26.4±1.78	26.4±1.77
<b>CDR global score, n (%)</b>			
0.5	544 (99.8)	546 (99.8)	554 (99.8)
1	1 (0.2)	1 (0.2)	0
<b>CDR-SB score, mean ± SD</b>	2.40±1.012	2.43±1.014	2.40±1.009
<b>ADAS-Cog 13 score, mean ± SD</b>	22.5±6.56	22.5±6.30	22.4±6.54
<b>ADCS-ADL-MCI score, mean ± SD</b>	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.

# ENGAGE: Patient disposition

Randomized	ENGAGE (N=1653)		
Dosed	n=1647		
	Placebo n=545	Low dose n=547	High dose n=555
<b>Discontinued treatment<sup>a</sup>, n (%)</b>	<b>96 (17.6)</b>	<b>105 (19.2)</b>	<b>148 (26.7)</b>
Adverse event	26 (4.8)	43 (7.9)	64 (11.5)
Consent withdrawn	14 (2.6)	11 (2.0)	15 (2.7)
Death	0	3 (0.5)	1 (0.2)
Study visit burden	4 (0.7)	3 (0.5)	9 (1.6)
Site terminated by sponsor	16 (2.9)	16 (2.9)	24 (4.3)
Other	28 (5.1)	22 (4.0)	28 (5.0)
<b>Withdrew from study<sup>a</sup>, n (%)</b>	<b>58 (10.6)</b>	<b>60 (11.0)</b>	<b>78 (14.1)</b>
Adverse event	16 (2.9)	23 (4.2)	26 (4.7)
Consent withdrawn	21 (3.9)	14 (2.6)	23 (4.1)
Death	0	3 (0.5)	2 (0.4)
Study visit burden	5 (0.9)	3 (0.5)	11 (2.0)
Site terminated by sponsor	2 (0.4)	1 (0.2)	0
Other	5 (0.9)	5 (0.9)	9 (1.6)
<b>Completed placebo-controlled period, n (%)</b>	<b>319 (58.5)</b>	<b>314 (57.4)</b>	<b>275 (49.5)</b>

ITT population. <sup>a</sup>Some categories with less than 1% patients are not displayed, including lost to follow-up, disease progression, pregnancy, investigator decision, relocation, change of treatment, withdrawal by parent/guardian, protocol amendment, site terminated by investigator and loss of capacity. ITT, intent to treat.

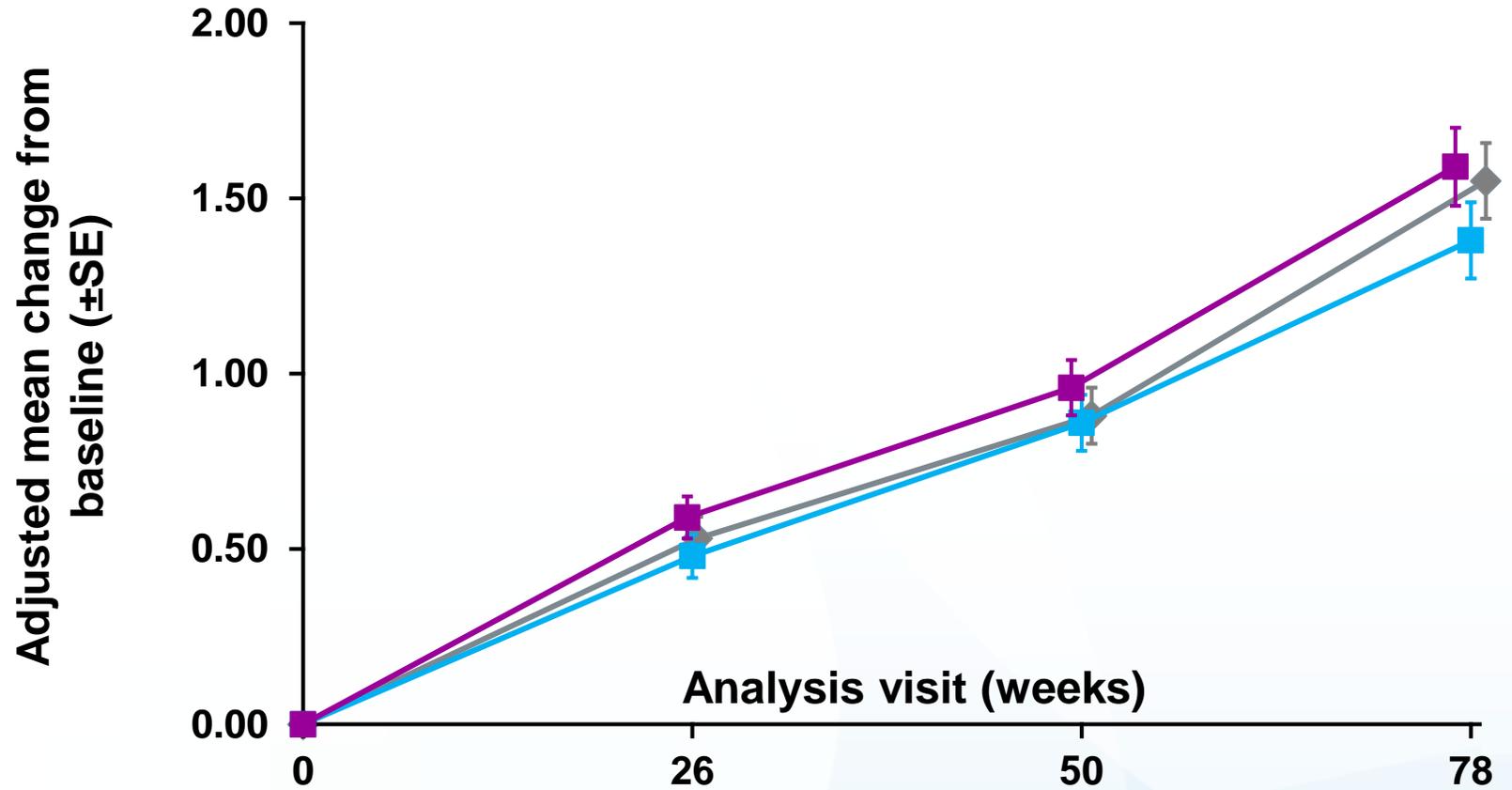
# ENGAGE: Primary and secondary endpoints from larger data set at Week 78

	Placebo decline (n=545)	Difference vs. placebo (%) <sup>a</sup> p-value <sup>b</sup>	
		Low dose (n=547)	High dose (n=555)
<b>CDR-SB</b>	1.55	<b>-0.18</b> (-12%) 0.2362	<b>0.03</b> (2%) 0.8252
<b>MMSE</b>	-3.5	<b>0.2</b> (-6%) 0.4875	<b>-0.1</b> (3%) 0.7961
<b>ADAS-Cog 13</b>	5.171	<b>-0.590</b> (-11%) 0.2475	<b>-0.605</b> (-12%) 0.2446
<b>ADCS-ADL-MCI</b>	-3.8	<b>0.7</b> (-18%) 0.1345	<b>0.7</b> (-18%) 0.1520

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

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

# ENGAGE: Longitudinal change from baseline in CDR-SB

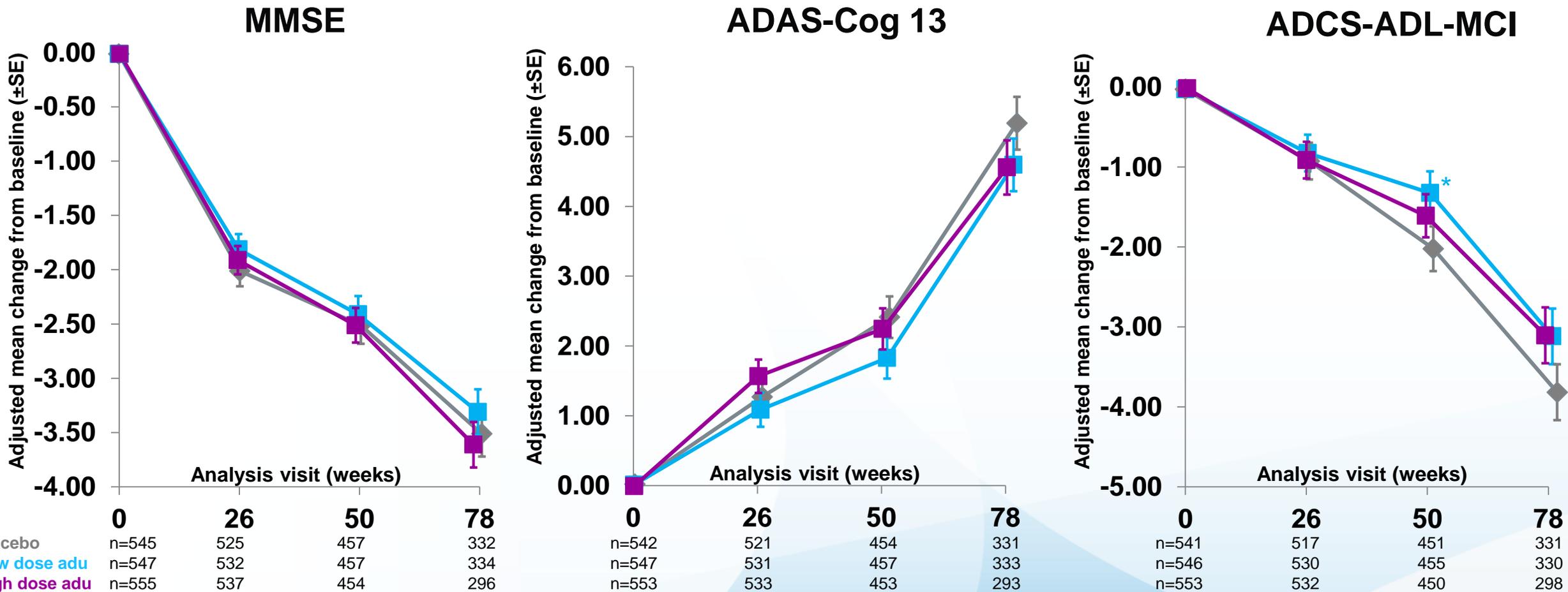


Placebo	n=545	522	455	333
Low dose aducanumab	n=547	529	454	331
High dose aducanumab	n=554	532	448	293

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.

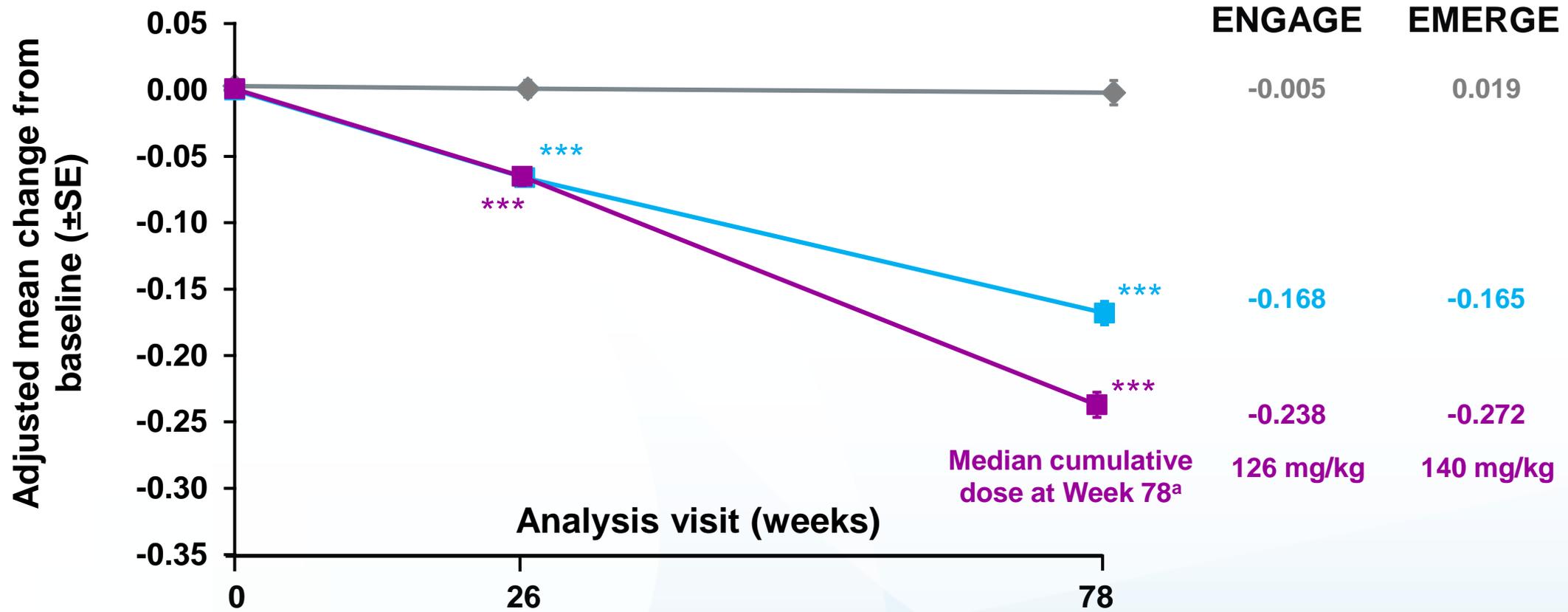
ApoE, apolipoprotein E; CDR-SB, Clinical Dementia Rating–Sum of Boxes; ITT, intent to treat; MMRM, mixed model for repeated measure; MMSE, Mini Mental State Examination; SE, standard error.

# ENGAGE: Longitudinal change from baseline in MMSE, ADAS-Cog 13 and ADSC-ADL-MCI



ITT population. \*p <0.05 compared with placebo (nominal). Values at each time point were based on an MMRM model, with change from baseline in MMSE, ADAS-Cog 13, or ADCS-ADL-MCI as the dependent variable and with fixed effects of treatment group, categorical visit, treatment-by-visit interaction, baseline measure, baseline measure by visit interaction, Alzheimer's disease symptomatic medication use at baseline, region, and laboratory ApoE ε4 status. 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); ApoE, apolipoprotein E; ITT, intent to treat; MMRM, mixed model for repeated measure; MMSE, Mini Mental State Examination; SE, standard error.

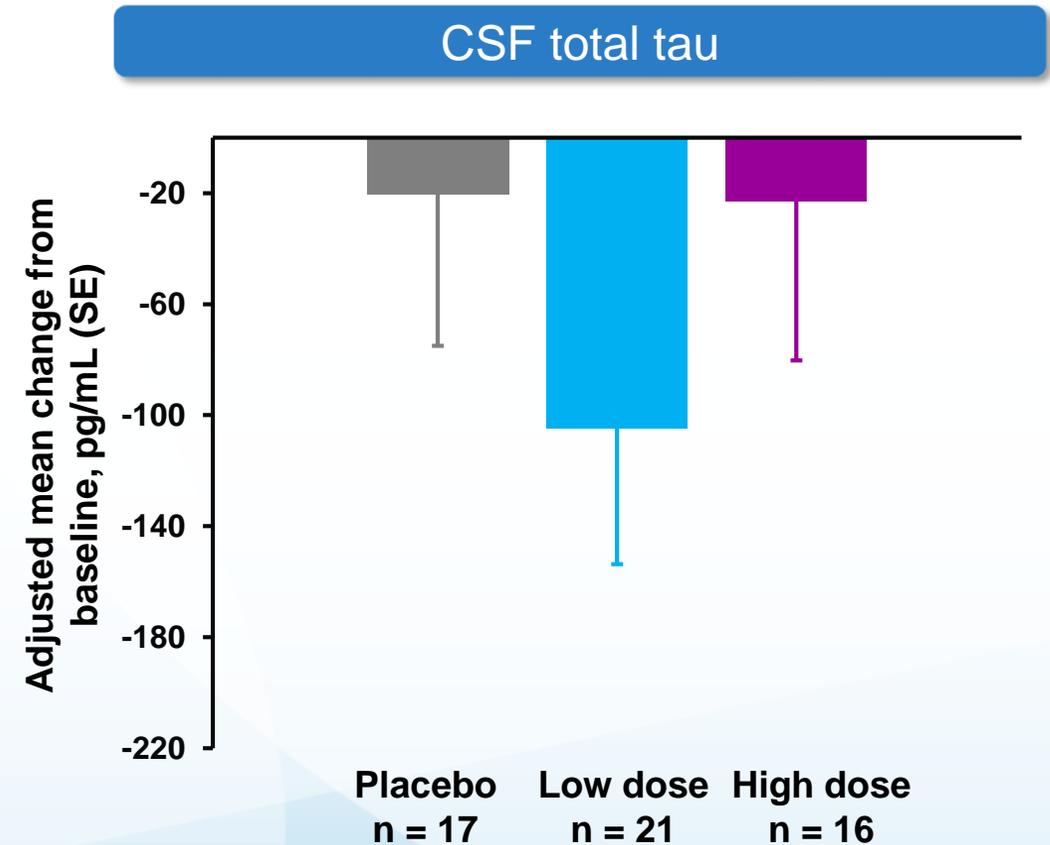
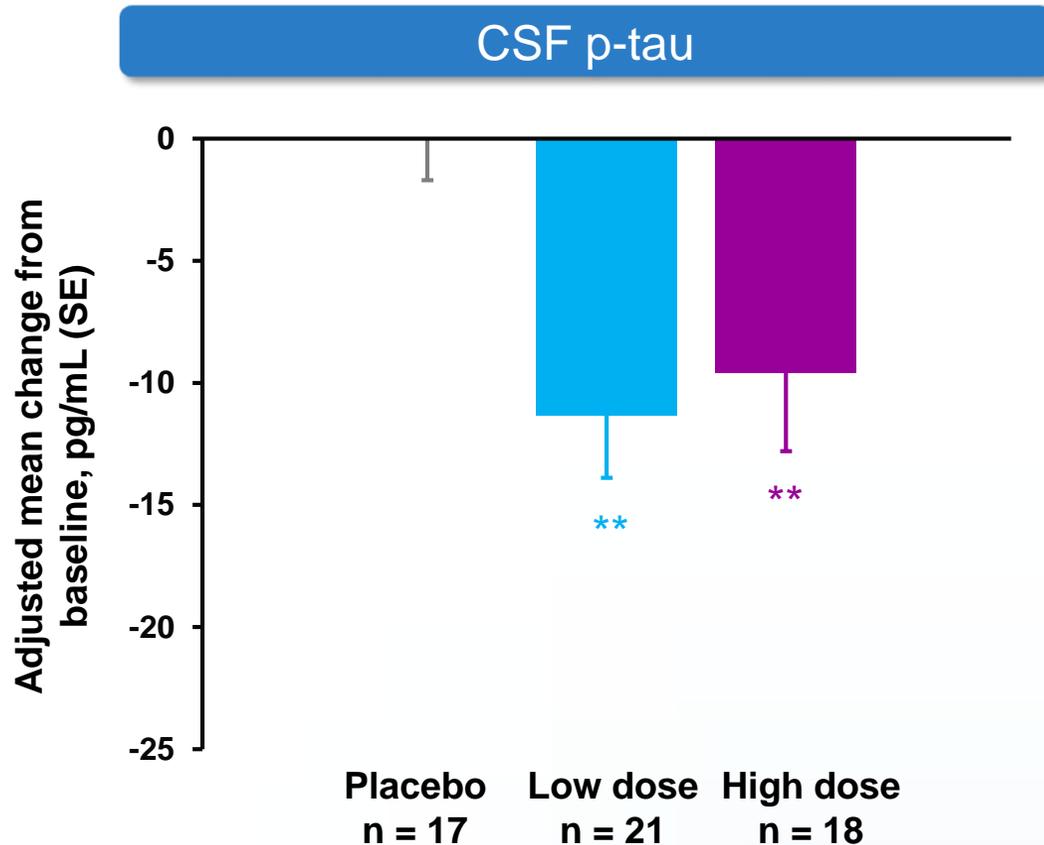
# ENGAGE: Longitudinal change from baseline in amyloid PET SUVR



	0	26	78
Placebo	n=203	164	104
Low dose aducanumab	n=198	166	116
High dose aducanumab	n=181	149	97

<sup>a</sup>Calculated from patients with Week 78 PET assessment. <sup>18</sup>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.

# ENGAGE: CSF biomarkers of tau pathology and neurodegeneration



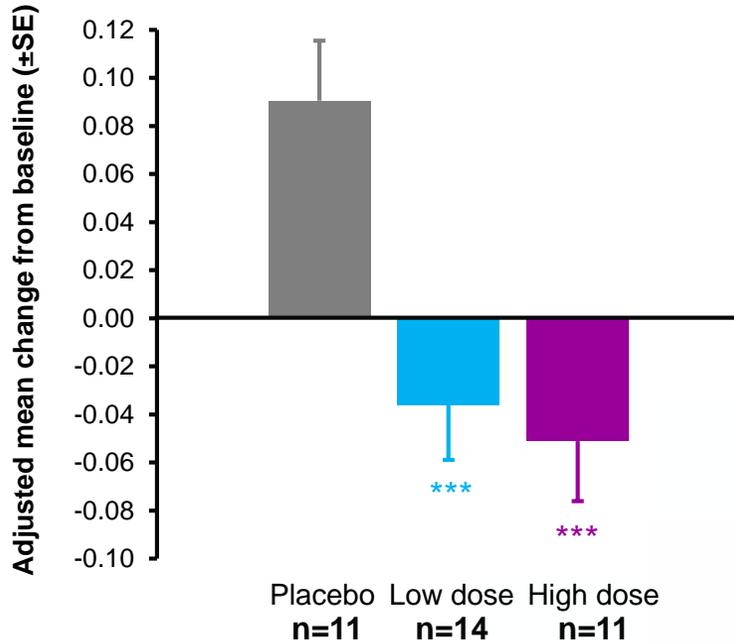
CSF modified analysis population (patients with both baseline and post-baseline CSF assessments). \*\*p<0.01 compared with placebo (nominal). Values were based on an ANCOVA model at Week 78, fitted with change from baseline as the dependent variable, and with categorical treatment, baseline biomarker value, baseline age, and laboratory ApoE  $\epsilon$ 4 status (carrier and non-carrier) as the independent variables. ANCOVA, analysis of covariance; ApoE, apolipoprotein E; CSF, cerebrospinal fluid; SE, standard error.

# Phase 3 Results

Tau PET data

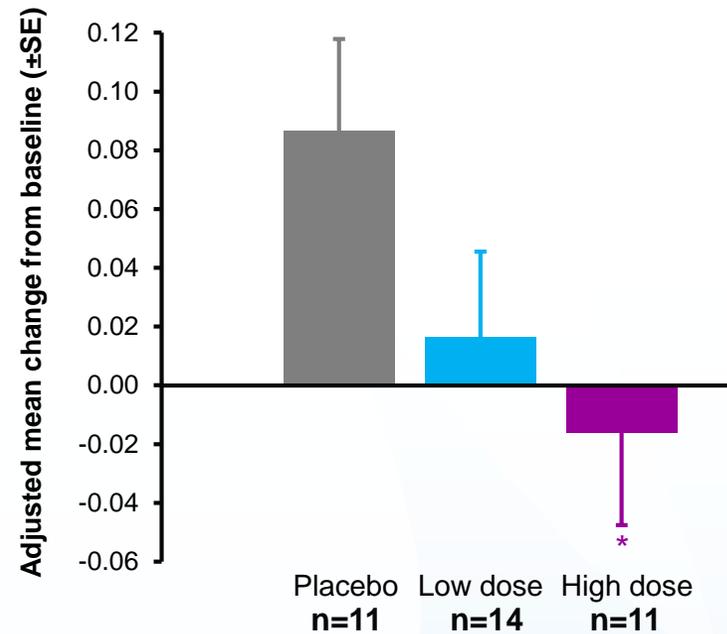
# EMERGE and ENGAGE: Composite SUVR change from baseline

## Medial temporal composite



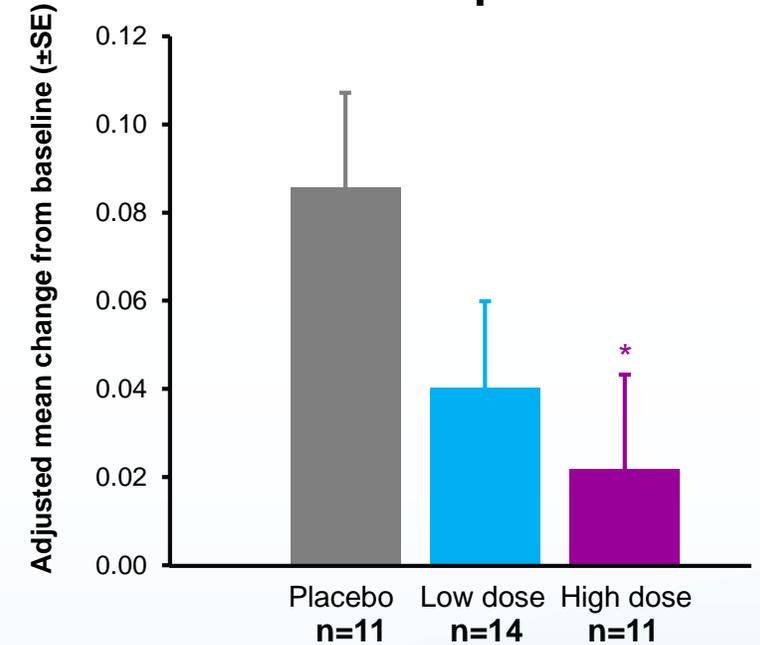
HIPPOCAMPUS  
 PARAHIPPOCAMPAL  
 TEMPORAL LOBE ANTERIOR MEDIAL  
 (includes Entorhinal and Amygdala)  
 TEMPORAL LOBE ANTERIOR LATERAL

## Temporal composite



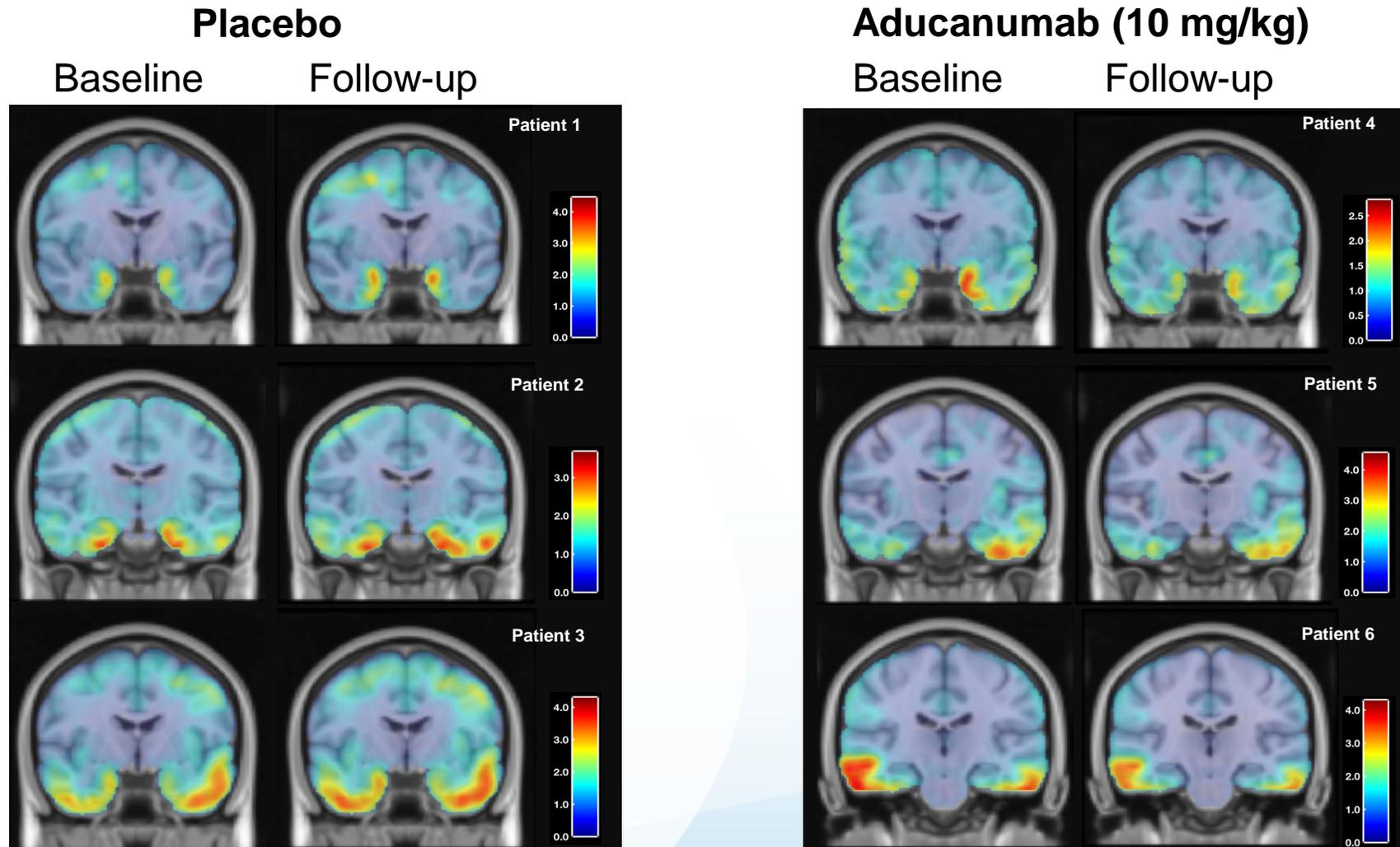
TEMPORAL LOBE Comprised of:  
 SUPERIOR, POSTERIOR, MIDDLE INFERIOR  
 POSTERIOR, SUPERIOR ANTERIOR,  
 FUSIFORM GYRUS

## Frontal composite



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

# Tau deposition in representative patients



Representative images from 3 patients in placebo group and 3 patients in aducanumab high dose group.

# Phase 3 Results

## Safety

# EMERGE and ENGAGE: Safety summary

	EMERGE			ENGAGE		
	Placebo (n=547)	Low dose (n=544)	High dose (n=547)	Placebo (n=541)	Low dose (n=548)	High dose (n=558)
<b>Patients with an AE, n (%)</b>	<b>476 (87.0)</b>	<b>477 (87.7)</b>	<b>505 (92.3)</b>	<b>465 (86.0)</b>	<b>491 (89.6)</b>	<b>500 (89.6)</b>
<b>Patients with an SAE, n (%)</b>	<b>77 (14.1)</b>	<b>69 (12.7)</b>	<b>66 (12.1)</b>	<b>69 (12.8)</b>	<b>71 (13.0)</b>	<b>71 (12.7)</b>
<b>Patients permanently discontinuing treatment due to AE, n (%)</b>	<b>16 (2.9)</b>	<b>42 (7.7)</b>	<b>48 (8.8)</b>	<b>28 (5.2)</b>	<b>45 (8.2)</b>	<b>64 (11.5)</b>
<b>Patients permanently discontinuing treatment due to ARIA, n (%)</b>	<b>1 (0.2)</b>	<b>25 (4.6)</b>	<b>36 (6.6)</b>	<b>6 (1.1)</b>	<b>27 (4.9)</b>	<b>41 (7.3)</b>
<b>Number of all-cause deaths, n (%)</b>	<b>5 (0.9)</b>	<b>0</b>	<b>6 (1.1)</b>	<b>0</b>	<b>3 (0.5)</b>	<b>2 (0.4)</b>

**Safety analyses presented were based on the larger dataset and are ongoing.**

Safety population. Patients randomized to placebo who accidentally received active dose are summarized under active groups (4 in ENGAGE and 1 in EMERGE).

All safety data presented are from the placebo-controlled period.

AE, adverse event; ARIA, amyloid-related imaging abnormalities; SAE, serious adverse event.

# EMERGE and ENGAGE: Adverse events with incidence >10%

	EMERGE			ENGAGE		
	Placebo (n=547)	Low dose (n=544)	High dose (n=547)	Placebo (n=541)	Low dose (n=548)	High dose (n=558)
<b>Patients with any event, n (%)</b>	<b>476 (87.0)</b>	<b>477 (87.7)</b>	<b>505 (92.3)</b>	<b>465 (86.0)</b>	<b>491 (89.6)</b>	<b>500 (89.6)</b>
<b>ARIA-E (%)</b>	<b>12 (2.2)</b>	<b>140 (25.7)</b>	<b>186 (34.0)</b>	<b>16 (3.0)</b>	<b>139 (25.4)</b>	<b>198 (35.5)</b>
<b>Headache (%)</b>	<b>83 (15.2)</b>	<b>106 (19.5)</b>	<b>106 (19.4)</b>	<b>81 (15.0)</b>	<b>98 (17.9)</b>	<b>114 (20.4)</b>
<b>ARIA-H, microhemorrhage (%)</b>	<b>38 (6.9)</b>	<b>88 (16.2)</b>	<b>102 (18.6)</b>	<b>31 (5.7)</b>	<b>85 (15.5)</b>	<b>98 (17.6)</b>
<b>Nasopharyngitis (%)</b>	<b>90 (16.5)</b>	<b>70 (12.9)</b>	<b>87 (15.9)</b>	<b>67 (12.4)</b>	<b>64 (11.7)</b>	<b>66 (11.8)</b>
<b>ARIA-H, superficial siderosis (%)</b>	<b>14 (2.6)</b>	<b>50 (9.2)</b>	<b>73 (13.3)</b>	<b>10 (1.8)</b>	<b>48 (8.8)</b>	<b>86 (15.4)</b>
<b>Fall (%)</b>	<b>68 (12.4)</b>	<b>64 (11.8)</b>	<b>69 (12.6)</b>	<b>55 (10.2)</b>	<b>77 (14.1)</b>	<b>83 (14.9)</b>

**This table includes patients who received at least one dose of investigational treatment.**

Safety population. Patients randomized to placebo who accidentally received active dose are summarized under active groups (4 in ENGAGE and 1 in EMERGE).

All safety data presented are from the placebo-controlled period.

ARIA-E, amyloid related imaging abnormality-edema/effusion; ARIA-H, amyloid related imaging abnormality-micro-hemorrhages and hemosiderin deposits.

# EMERGE and ENGAGE: ARIA incidence

	EMERGE			ENGAGE		
	Placebo (n=544)	Low dose (n=537)	High dose (n=541)	Placebo (n=533)	Low dose (n=544)	High dose (n=554)
<b>ARIA-E<sup>a</sup>, n/total (%)</b>	<b>12/544 (2.2)</b>	<b>140/537 (26.1)</b>	<b>186/541 (34.4)</b>	<b>16/533 (3.0)</b>	<b>139/544 (25.6)</b>	<b>198/554 (35.7)</b>
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)
<b>ARIA-H, microhemorrhage, n (%)</b>	<b>38 (7.0)</b>	<b>88 (16.4)</b>	<b>102 (18.9)</b>	<b>31 (5.8)</b>	<b>85 (15.6)</b>	<b>98 (17.7)</b>
<b>ARIA-H, superficial siderosis, n (%)</b>	<b>14 (2.6)</b>	<b>50 (9.3)</b>	<b>73 (13.5)</b>	<b>10 (1.9)</b>	<b>48 (8.8)</b>	<b>86 (15.5)</b>
<b>ARIA-H, macrohemorrhage, n (%)</b>	<b>0</b>	<b>1 (0.2)</b>	<b>3 (0.6)</b>	<b>4 (0.8)</b>	<b>0</b>	<b>3 (0.5)</b>

**This table includes patients who had at least one post-baseline safety MRI.**

Safety MRI population (patients with at least one post-baseline MRI). <sup>a</sup>ARIA-E with or without ARIA-H.

All safety data presented are from the placebo-controlled period.

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

# EMERGE and ENGAGE: ARIA incidence

	EMERGE			ENGAGE		
	Placebo (n=544)	Low dose (n=537)	High dose (n=541)	Placebo (n=533)	Low dose (n=544)	High dose (n=554)
<b>Any ARIA (either E or H), n (%)</b>	<b>56 (10.3)</b>	<b>176 (32.8)</b>	<b>223 (41.2)</b>	<b>52 (9.8)</b>	<b>167 (30.7)</b>	<b>223 (40.3)</b>
<b>Symptomatic status, n (%)</b>	<b>56</b>	<b>176</b>	<b>223</b>	<b>52</b>	<b>167</b>	<b>223</b>
Asymptomatic ARIA	53 (94.6)	138 (78.4)	179 (80.3)	49 (94.2)	139 (83.2)	158 (70.9)
Symptomatic ARIA	3 (5.4)	38 (21.6)	44 (19.7)	3 (5.8)	28 (16.8)	65 (29.1)

**This table includes patients who had at least one post-baseline safety MRI.**

- 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

Safety MRI population (patients with at least one post-baseline MRI). All safety data presented are from the placebo-controlled period.

ARIA, amyloid-related imaging abnormalities; ARIA-E, amyloid-related imaging abnormalities due to vasogenic edema; ARIA-H, amyloid-related imaging abnormalities due to microhemorrhage, superficial siderosis or macrohemorrhage.

# EMERGE and ENGAGE

# Defining a population by Protocol Version 4 (PV4)

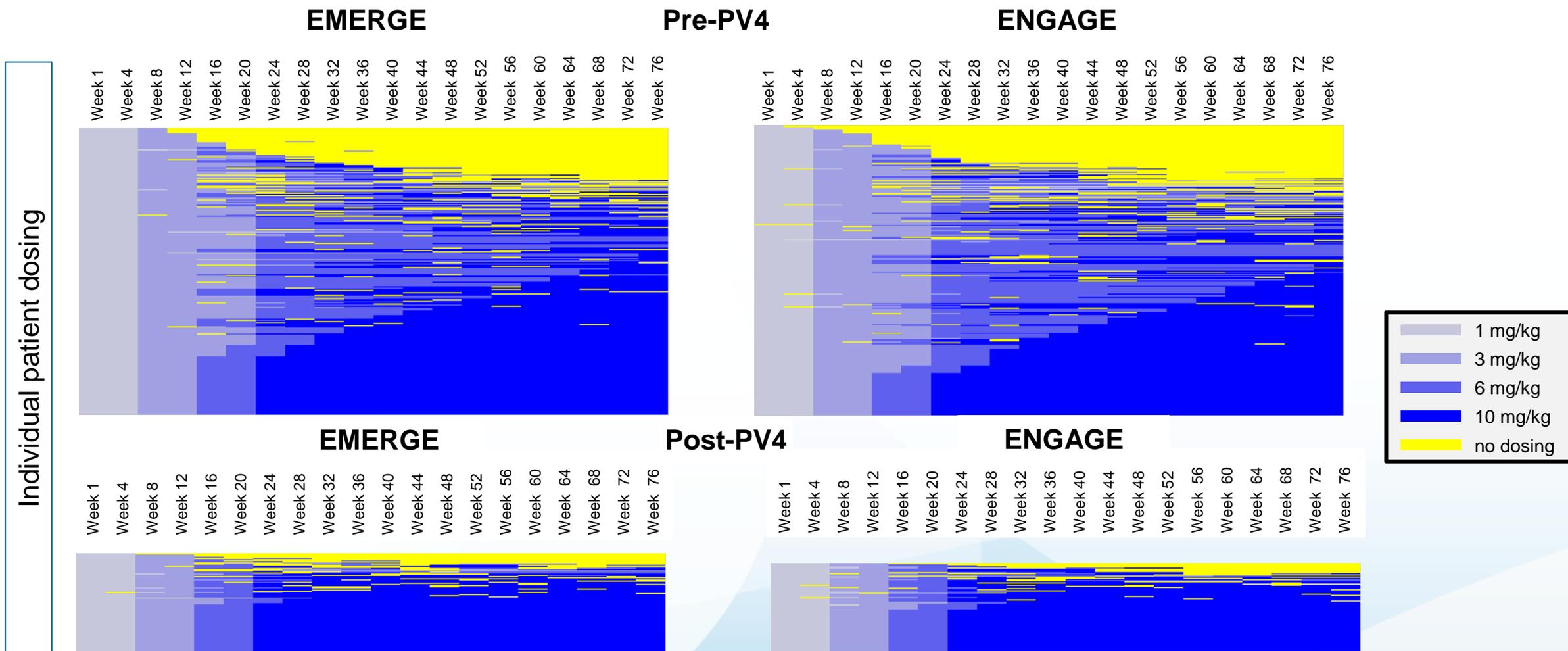
## Patients selected using the cutoff related to PV4:

- (1) To assess the treatment effect under the intended dosing regimen and ARIA management
- (2) To assess the treatment effect among a representative population (i.e., ApoE  $\epsilon$ 4 carriers consist of  $\sim 2/3$  of the population in AD)
- (3) To preserve the randomization

		Median cumulative dose at Week 78
Post- PV4	ApoE $\epsilon$ 4 + : opportunity to receive 14 doses of 10 mg/kg after PV4 consent	153 mg/kg (post-PV4)
	ApoE $\epsilon$ 4 - : opportunity to receive 14 doses of 10 mg/kg after PV4 consent	
Pre- PV4	ApoE $\epsilon$ 4 + : opportunity to receive 6 mg/kg before PV4 consent	116 mg/kg (pre-PV4)
	ApoE $\epsilon$ 4 + : opportunity to receive 0-13 doses of 10 mg/kg after PV4 consent	
	ApoE $\epsilon$ 4 - : opportunity to receive 10 mg/kg before PV4 consent	

# EMERGE and ENGAGE: Individual-level dosing in high dose regimen

- For pre-PV4 patients, 21% in EMERGE and 15% in ENGAGE received the full possible 14 doses of 10 mg/kg
- For post-PV4 patients, 51% in EMERGE and 47% in ENGAGE received the full possible 14 doses of 10 mg/kg



OTC population. Patients who had the opportunity to complete Week 78 visit by March 20, 2019.  
 OTC, opportunity to complete; PV4, Protocol, Version 4.

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

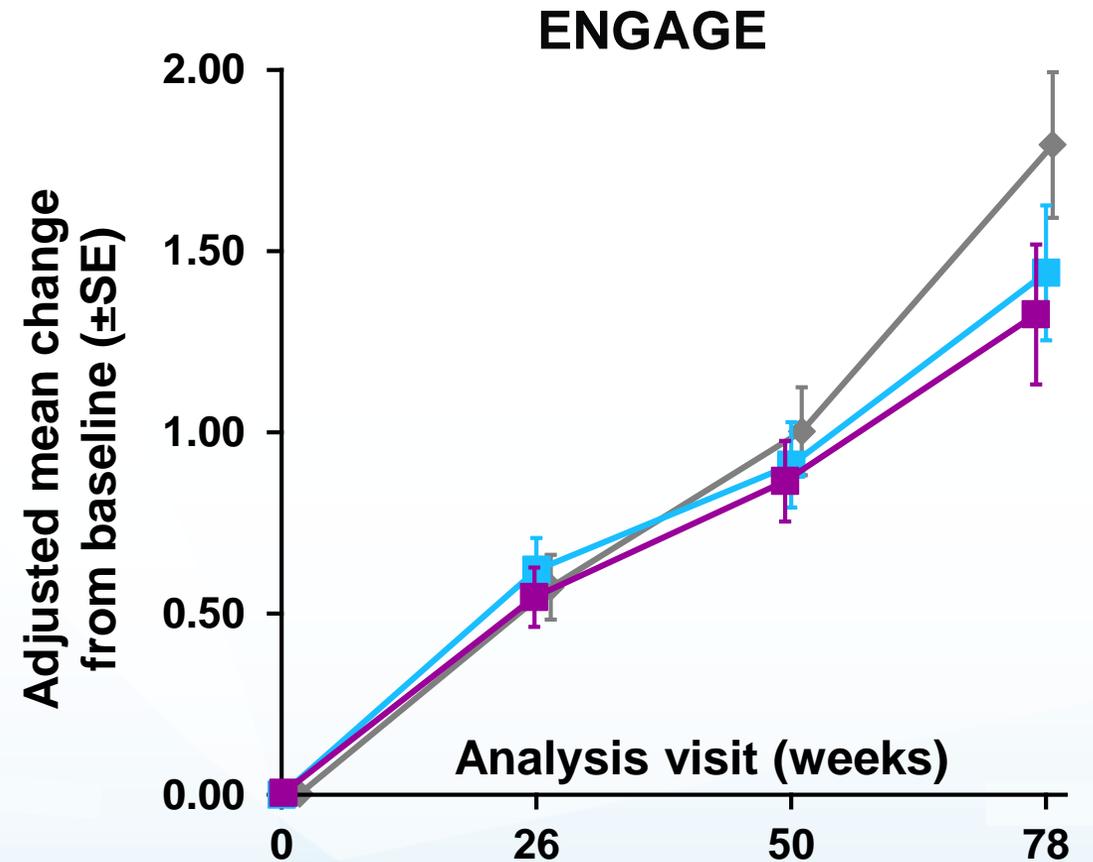
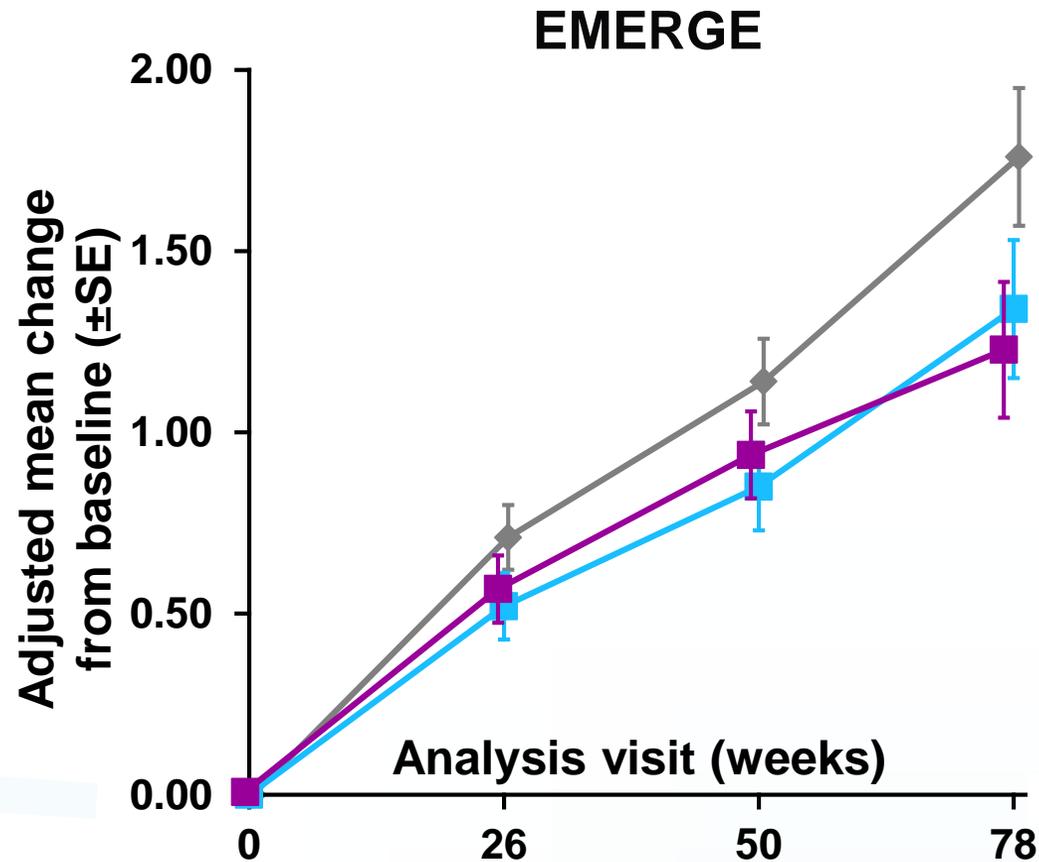
## ITT

## Post-PV4<sup>a,b</sup>

EMERGE	Placebo decline (n=548)	Low dose (n=543)	High dose (n=547)	Placebo decline (n=304)	Low dose (n=295)	High dose (n=288)
		diff vs. placebo, 95% CI (%) <sup>c</sup>	diff vs. placebo 95% CI (%) <sup>c</sup>		diff vs. placebo 95% CI (%) <sup>c</sup>	diff vs. placebo 95% CI (%) <sup>c</sup>
CDR-SB	1.74	<b>-0.25</b> -0.55, 0.06 (-14%)	<b>-0.40</b> -0.71, -0.10 (-23%)	1.76	<b>-0.42</b> -0.94, 0.10 (-24%)	<b>-0.53</b> -1.05, -0.02 (-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	1.55	<b>-0.18</b> -0.47, 0.12 (-12%)	<b>0.03</b> -0.26, 0.33 (2%)	1.79	<b>-0.35</b> -0.88, 0.18 (-20%)	<b>-0.48</b> -1.02, 0.06 (-27%)

<sup>a</sup>MMRM model was fitted separately for pre- and post-Protocol Version 4 set; <sup>b</sup>Patients who consented to PV4 or higher version prior to Week 16 in ITT population; <sup>c</sup>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.

# Post PV4<sup>a,b</sup>: Longitudinal change from baseline in CDR-SB



	0	26	50	78
Placebo	n=303	293	198	74
Low dose aducanumab	n=295	280	197	76
High dose aducanumab	n=288	271	200	80

	0	26	50	78
Placebo	n=247	236	174	66
Low dose aducanumab	n=261	251	185	82
High dose aducanumab	n=282	276	204	69

<sup>a</sup>MMRM model was fitted separately for pre- and post-Protocol Version 4 set; <sup>b</sup>Patients who consented to PV4 or higher version prior to Week 16 in ITT population. CDR-SB, Clinical Dementia Rating–Sum of Boxes; PV4, Protocol Version 4; SE, standard error.

# 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 ENGAGE, aducanumab did not reduce clinical decline
  - In a post hoc analysis, data from a subset of patients exposed to high dose aducanumab support the positive findings of EMERGE
- In sub-studies, aducanumab showed an effect on disease related biomarkers
- The most common AEs were ARIA-E and headache
- Site activation has initiated in the US for the re-dosing study, EMBARK, with the aim to offer access to aducanumab to eligible patients previously enrolled in the aducanumab clinical studies

# Acknowledgments

- We thank all patients and family members who participated in the aducanumab studies and the investigators and staff who conducted these studies, DSMB, and steering committee members
- We also thank those who contributed to this work, including Kimberly Umans, Stacy Lindborg, John O’Gorman, Xiaopeng Miao, Charlie Cao, Carmen Castrillo-Viguera, Ping He, Carol Yurgalevitch, Ivana Rubino, and Eric Ponton

