### P57496

Subgroup Analyses of the Amyloid PET Substudies From EMERGE and ENGAGE, Phase 3 Clinical Trials Evaluating Aducanumab in Patients With Early Alzheimer's Disease

## OBJECTIVE

 To examine the effects of aducanumab treatment on brain Aβ plaque levels in prespecified subgroups of patients defined by baseline characteristics in the Phase 3 clinical trials

# CONCLUSIONS

- In the Phase 3 EMERGE and ENGAGE studies, aducanumab treatment was associated with dosedependent reduction in brain Aβ plaque levels in patients with early Alzheimer's disease.
- Robust dose-dependent lowering of brain Aβ plaque levels was observed across all prespecified patient subgroups defined by ApoE ε4 status, baseline clinical stage (MCI due to Alzheimer's disease or mild Alzheimer's disease dementia), baseline severity (MMSE), use of Alzheimer's disease symptomatic medications at baseline, age, and sex for both the low-and high-dose aducanumab treatment groups.

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### Introduction

- The accumulation of A $\beta$  plaques in the brain is a defining pathophysiological feature of Alzheimer's disease.<sup>1</sup>
- Aducanumab is a human, immunoglobulin γ1 monoclonal antibody directed against aggregated soluble and insoluble forms of Aβ.<sup>2.3</sup>
- Aducanumab is the first FDA-approved Alzheimer's disease treatment that reduces Aβ plaques, a defining pathophysiological feature of Alzheimer's disease.<sup>3</sup>
- A robust dose-dependent reduction in brain Aβ plaque levels, as measured by amyloid PET, was demonstrated across aducanumab clinical studies (PRIME, NCT01677572; EMERGE, NCT02484547; and ENGAGE, NCT02477800).<sup>2,4</sup>
- Here, we report the results of subgroup analysis of amyloid PET composite SUVR across prespecified patient subgroups defined by ApoE ε4 status, baseline clinical stage (MCI due to Alzheimer's disease or mild Alzheimer's disease dementia), baseline severity (MMSE), use of Alzheimer's disease symptomatic medications at baseline, age, and sex in the EMERGE and ENGAGE Phase 3 clinical trials evaluating aducanumab in patients with early Alzheimer's disease.

#### Results

 In the overall PET substudy population, the mean (SD) baseline amyloid PET composite SUVR was 1.375 (0.1748) with placebo, 1.394 (0.1837) with low dose, and 1.383 (0.1833) with high dose in EMERGE and 1.376 (0.1990) with placebo, 1.385 (0.1859) with low dose, and 1.407 (0.1786) with high dose in ENGAGE.

• In both EMERGE and ENGAGE, aducanumab treatment was associated with robust dosedependent reduction in brain A $\beta$  levels. The magnitude of treatment effect on amyloid PET composite SUVR relative to placebo at Week 78 was -0.179 with low dose and -0.278 with high dose in EMERGE and -0.167 with low dose and -0.232 with high dose in ENGAGE.

 In all 13 prespecified subgroups defined by the 6 baseline factors, statistically significant reduction in amyloid PET composite SUVR favoring both the low- and high-dose aducanumab treatments relative to placebo was observed in both EMERGE and ENGAGE (Figure).

- · The treatment effect on amyloid PET composite SUVR was:
  - Dose-dependent with a greater reduction observed in the high-dose group relative to the low-dose group in all 13 subgroups in both EMERGE and ENGAGE.
  - Greater in the EMERGE high-dose group relative to the ENGAGE high-dose group in 11 of 13 subgroups, consistent with the results in the overall PET substudy population, in which the mean cumulative dose in the high-dose group was greater in EMERGE (118.3 mg/kg) than in ENGAGE (109.1 mg/kg).
  - Greater in ApoE ε4 noncarriers relative to carriers. This finding is a direct result of the dosing regimen<sup>a,b</sup> and study protocol amendments.<sup>b</sup>
  - Accounting for these differences, PK/SUVR modeling demonstrated that the magnitude of reduction in amyloid PET composite SUVR was comparable across carrier status.
  - Comparable across a range of disease severity when analyzed by clinical stage, MMSE, and Alzheimer's disease medication use at baseline for respective dose groups across the 2 studies.
  - Observed across all age groups examined with a trend of greater magnitude of effect with increasing age.
  - · Comparable in both men and women in both studies.
- The results in each of the subgroup of patients were consistent with the findings in the overall PET substudy population, in which a statistically significant dose-dependent reduction in brain Aβ plaque levels was observed.

### Methods

 EMERGE and ENGAGE were 18-month, randomized, double-blind, placebo-controlled, Phase 3 studies evaluating aducanumab in patients with early Alzheimer's disease with evidence of amyloid pathology.

- Patients were randomized (1:1:1) to receive high-dose aducanumab, low-dose aducanumab, or placebo intravenously every 4 weeks.<sup>4</sup>
- Longitudinal amyloid PET imaging using <sup>18</sup>F-florbetapir was performed in a subset of patients (n=488 in EMERGE; n=585 in ENGAGE) at Screening, Week 26, and Week 78.<sup>4</sup>
- Subgroup analysis of amyloid PET composite SUVR for 6 prespecified factors consisting of ApoE ε4 status (carrier or noncarrier), baseline clinical stage (MCI due to Alzheimer's disease or mild Alzheimer's disease dementia), baseline MMSE (≤26 or ≥27), use of Alzheimer's disease symptomatic medications at baseline (yes or no), age (≤64, 65 to 74, or ≥75 years) and sex (male or female) for a total of 13 subgroups was conducted for each study.

#### Figure. Results of subgroup analysis of amyloid PET composite SUVR for 6 prespecified factors

		Week 78		Week 78
	Number of participants (at baseline, at Week 78)	Favors aducanumab	Number of participants (at baseline, at Week 78)	Favors aducanumab
ApoE4 status	Carrier (105, 69)	•••	Carrier (130, 85)	H <b>-</b> H
	Noncarrier (65,40)	• I	Noncarrier (53, 27)	<b></b>
Basline clinical stage	e MCI due to AD (140, 92)	HeH	MCI due to AD (153, 94)	H
	Mild AD (30, 17)		Mild AD (30, 18)	
Baseline MMSE	MMSE ≥27 (74, 78)	<b>→→</b>	MMSE ≥27 (81, 51)	H <b>O</b> H
	MMSE ≤26 (92, 57)	<b>⊷</b> ⊷	MMSE ≤26 (102, 61)	H <b>H</b> H
Baseline AD	Yes (72, 79)	H-H-I	Yes (95, 56)	H <b>-</b> H
medication use	No (87, 91)	<b></b>	No (88, 56)	H <b>-</b> -1
Age Sex	≤64 (31, 36)	<b>⊢⊷</b>	≤64 (48, 29)	<b></b>
	65-74 (73, 74)	<b>→→</b>	65-74 (77, 52)	H <b>0</b> H
	≥75 (55, 60)	►	≥75 (58, 31)	<b></b>
	Female (76, 90)	H <b>H</b>	Female (101, 58)	H <b>-</b> H
	Male (83, 80)	••	Male (82, 54)	H <b>H</b> H
	.0.4	-0.3 -0.2 -0.1 0.0	.0.4	-0.3 -0.2 -0.1
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	Amyloid PET composite 5 change from baseli (95% CI for dii	SUVR adjusted mean ine vs placebo fference) Week 78	change from bas (95% CI for	difference)
	Amyloid PET composite 3 change from baseli (95% CI for di	SUVR adjusted mean ine vs placebo fference) Week 78 Favors	change from bas change from bas (95% Cl for	eline vs placebo difference) Week 78 Favors
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ApoE4 status Basline clinical stag	Amyloid PET composite 5 change from basel (95% CI for di (at baseline, at Week 78) Carrier (108, 71) Noncarrier (53, 29) M Clu du to AD (132, 85)	SUVR adjusted mean ine vs placebo fference) Week 78 Favors aducanumab	Number of participants (35% Ct for Number of participants (at baseline, at Week 78) Carrier (148, 104) Noncarrier (50.4) MCI due to AD (169, 120)	Week 78 Favors aducanumab
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\*Low dose: Titration to 3 mg/kg for ApoE E4+ patients and 6 mg/kg for ApoE E4- patients; \*Hgh dose: Titration to 10 mg/kg for al patients (protocol version 4 and above); titration to 6 mg/kg for ApoE E4+ patients and 10 mg/kg for ApoE E4- patients (prior to protocol version 4). Abbreviations AB, amyloid beta, AD, Abbremer's disease; ApoE, apolipoprotein F; FDA, US Food and Drug Administration, MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; PET, positron emission tomography; PK, pharmacobine; SUVR, standardized uptake value ratio. References 1. Jack R, et al. *Alzimiteriners Demens* 2016;14:535-565; 2. Sevigny, et al. Nature. 2016;535-566; 3. Adultein; Prescribing information. Biogen, Inc.; 2021; 4. US Food and Drug Administration. Combined FDA and applications advisory; Committee biefing document. Accessed July 9, 2021. https://www.tda.gov/meda/143502/download Disclosures RR, TC, YT, LN, CC-V, PH, and SBH are employees of Biogen. HW is an employee of Cytel. This study was sponsored by Biogen. (Cambridge, MA, USA). Writing and editorial support for the preparation of this poster was provided by MedTech Meda, Ltd (Atlanta, GA, USA); funding was provided by Biogen.

laboratory ApoE £4 status (if any of these covariates was not the subgroup factor in that specific analysis).