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

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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 dose-dependent 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 Aβ plaques in the brain is a defining pathophysiological feature of Alzheimer's disease.[1]
- Aducanumab is a human, immunoglobulin γ1 monoclonal antibody directed against aggregated soluble and insoluble forms of Aβ.[2,3]
- Aducanumab is the first FDA-approved Alzheimer's disease treatment that reduces Aβ plaques, a defining pathophysiological feature of Alzheimer's disease.[3]
- 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).[2,4]
- 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.

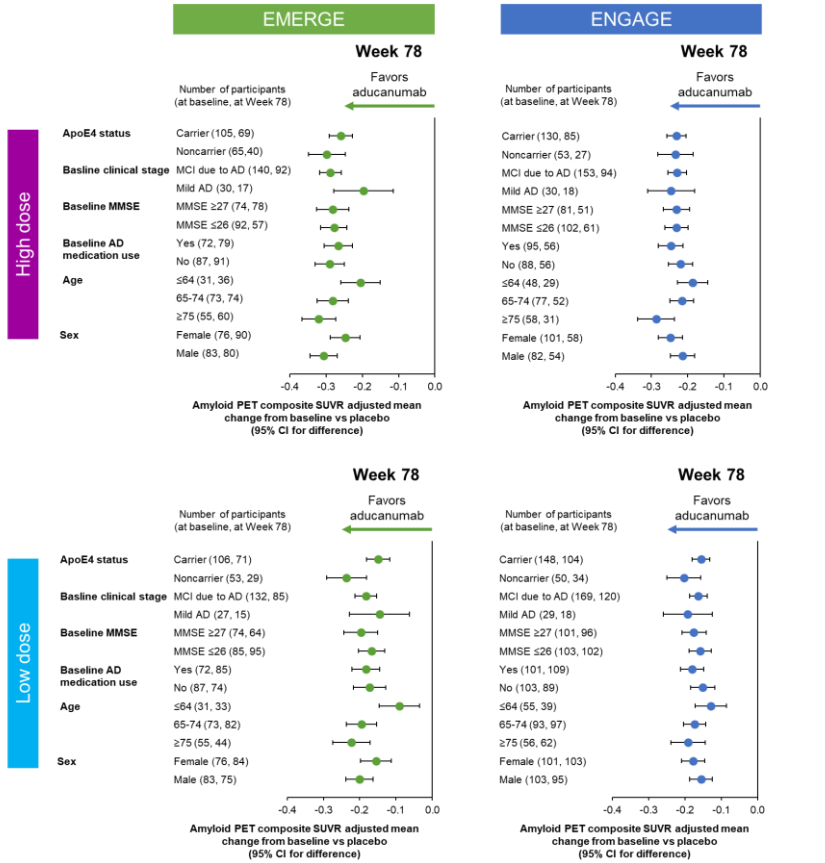
Methods

- 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.[4]
- Longitudinal amyloid PET imaging using ^{18}F-florbetapir was performed in a subset of patients (n=488 in EMERGE; n=585 in ENGAGE) at Screening, Week 26, and Week 78.[4]
- 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.

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 dose-dependent reduction in brain Aβ 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[a,b] and study protocol amendments.[b]
    - 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.

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



Results were based on a mixed model for repeated measures (MMRM) model for each subgroup, with change from baseline as dependent variable and with fixed effects of treatment group, categorical visit, treatment-by-visit interaction, baseline SUVR value, baseline SUVR value by visit interaction, baseline MMSE, baseline age, and baseline laboratory ApoE ε4 status (if any of these covariates was not the subgroup factor in that specific analysis).

[a]Low dose: Titration to 3 mg/kg for ApoE ε4+ patients and 6 mg/kg for ApoE ε4− patients; [b]High dose: Titration to 10 mg/kg for all patients (protocol version 4 and above); titration to 6 mg/kg for ApoE ε4+ patients and 10 mg/kg for ApoE ε4− patients (prior to protocol version 4).

Abbreviations Aβ, amyloid beta; AD, Alzheimer's disease; ApoE, apolipoprotein E; FDA, US Food and Drug Administration; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; PET, positron emission tomography; PK, pharmacokinetics; SUVR, standardized uptake value ratio.

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