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Conclusions
- At 24 months, in this subgroup analysis of ApoE ε4 carriers from both fixed-dose and titration cohorts, amyloid plaque levels continued to decrease.
- The clinical endpoints, CDR-SB and MMSE, suggest continued benefit of aducanumab treatment in ApoE ε4 carriers over 24 months.
- No new safety signals were identified in ApoE ε4 carriers.
- These data continue to support further investigation of the clinical efficacy and safety of aducanumab in patients with early AD in the ENGAGE and EMERGE Phase 3 trials.

Introduction
- Aducanumab binds to both soluble and insoluble aggregated forms of Aβ, including oligomers, protofibrils, and fibrils.1
- Treatment with aducanumab in the Phb study (PRIME) resulted in a time and dose dependent removal of plaques from the brain as shown by positron emission tomography (PET) standardized uptake value ratio.1
- Patients with early AD enrolled in PRIME experienced a sustained delay in the disease progression as measured by exploratory clinical endpoints at 12, 24 and 36 months.1
- Here, we report 24-month results from ApoE ε4 carriers in PRIME, including 12 months from the placebo-controlled period and 12 months from the long-term extension (LTE).

Objective
- To describe the effect of aducanumab on ApoE ε4 carriers from both fixed-dose and titration cohorts in the PRIME study.

Methods
- In this randomized, double-blind, placebo-controlled study (NCT01677572), patients (50–90 years; prodromal/ mild AD; positive florbetapir positron emission tomography [PET] read) were stratified 3:1 to cohorts of fixed aducanumab doses or placebo every 4 weeks for 52 weeks, stratified by ApoE ε4 status (Figure 1).
- After completion of fixed-dose cohort enrollment, a cohort consisting of only ApoE ε4 carriers and a corresponding placebo group was added who received titrated aducanumab (1 mg/kg [2 doses]; 3 mg/kg [4 doses]; 6 mg/kg [5 doses]; 10 mg/kg thereafter) or placebo (Figure 2).
- The average expected dose for patients in the titration cohort was 2.9 mg/kg, 5.3 mg/kg, and 7.6 mg/kg, by Week 24, Week 52, and Week 110, respectively.
- Patients meeting eligibility criteria at Week 56 were enrolled in the LTE, where all patients were assigned to receive aducanumab 3, 6, or 10 mg/kg, fixed or titrated (Figure 1).
- The primary endpoint in the LTE was safety/ tolerability.
- Exploratory endpoints included changes in amyloid PET and measures of clinical decline on the Clinical Dementia Rating-Sum of Boxes (CDR-SB) and Mini-Mental State Examination (MMSE).

Table 2. Incidence of ARIA in PC and LTE in ApoE ε4 carriers

<table>
<thead>
<tr>
<th>Group</th>
<th>PC (12 months)</th>
<th>LTE (12 months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>1 (1%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Aducanumab</td>
<td>0</td>
<td>0</td>
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</tbody>
</table>

Results
- 138 (70%) of 196 patients randomized and dosed in PRIME and 100 (70%) of the 343 patients dosed in the LTE were ApoE ε4 carriers.
- Baseline characteristics of ApoE ε4 carriers are shown in Table 1.
- ARIA occurred more frequently in ApoE ε4 carriers (n=17 [17%]) as compared with noncarriers (n=3 [7%]) in the LTE, the most common serious adverse event in ApoE ε4 carriers in the LTE was ARIA (n=4 [2%]).
- Incidence of ARIA in ApoE ε4 carriers switching from placebo to aducanumab in the LTE was consistent with that reported in the placebo-controlled portion of the study (Table 2).
- ApoE ε4 carriers who continued aducanumab treatment up to 24 months experienced continued reductions in brain amyloid plaque levels, as measured by PET (Figure 2).
- CDR-SB and MMSE data suggest clinical benefit on the rate of clinical decline in ApoE ε4 carriers continuing aducanumab over 24 months (Figure 3).