Aducanumab 48-month analyses from PRIME, a Phase 1b study in patients with early Alzheimer's disease

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Conclusions
• Amyloid plaque levels continued to decrease in a dos- and time-dependent manner in patients treated with aducanumab who completed the first three years of the long-term extension (LTE).
• Mean amyloid plaque levels in the 20 mg/kg fixed-dose cohort reached and remained at a standardized uptake value ratio (SUVR) level below 1.1, which is considered the quantitative cutpoint suggested to discriminate between a positive and negative scan.1
• Analysis of exploratory clinical endpoints Clinical Dementia Rating-Sum of Boxes (CDR-SB) and Mini Mental State Examination (MMSE) suggest clinical benefit in patients continuing aducanumab over 48 months.
• The safety profile of aducanumab remains unchanged.
• These data continue to support further investigation of the clinical efficacy and safety of aducanumab in patients with early Alzheimer’s disease (AD) in the ENGAGE and EMERGE Phase 3 trials.

Introduction
• Aducanumab (BIB037) is a human anti-amyloid beta monoclonal antibody that binds to both soluble and insoluble aggregated forms of amyloid beta, including oligomers, protofibrils, and fibrils.1,2
• PRIME is an ongoing Phase 1b study assessing the safety, tolerability, pharmacokinetics, and pharmacodynamics of aducanumab in patients with prodromal or mild AD.3
• Here, we report 48-month results from the fixed-dose cohorts of PRIME, including 12 months from the placebo-controlled period and 36 months from the LTE.

Objective
• To report amyloid positron emission tomography (PET) data and clinical data at 48 months follow up, including cumulative safety data for aducanumab as of the cutoff date of the most recent interim analysis.

Methods
• In this randomized, double-blind, placebo-controlled study (NCT016776727), patients (50–90 years old; prodromal/mild AD; positive for the AP18 or A14 PET read) were randomized: 3:1 to cohorts of fixed aducanumab doses or placebo.
• After completion of fixed-dose cohort enrollment, a cohort of ApoE ε4 carriers was added who received either aducanumab titrated to 10 mg/kg or placebo.
• As patients in the titration cohort have not yet completed the third year of the LTE, only data from patients originally assigned to fixed-dose cohorts during the placebo-controlled period are presented here.
• Patients meeting eligibility criteria at Week 56 could enroll in the LTE, where all patients were assigned to receive aducanumab 3, 6, or 10 mg/kg, fixed or titrated (Figure 2).
• The primary endpoint in PRIME is safety/tolerability.
• Exploratory endpoints in the LTE include changes in amyloid PET and measures of clinical decline such as CDR-SB and MMSE.

Results
48-month efficacy data for fixed-dose cohorts
• Of 165 patients randomized and dosed in PRIME within the fixed-dose cohorts, 117 were dosed in the LTE and 59 completed treatment at Month 48.
• Baseline characteristics are shown in Table 1.
• In patients treated up to 48 months, amyloid plaque levels as measured by PET continued to decrease in a dose- and time-dependent manner (Figure 2).
• Mean amyloid plaque levels in the 10 mg/kg fixed-dose treatment group reached and remained at an SUVR level below 1.1, which is considered a quantitative cutpoint suggested to discriminate between a positive and negative scan.1
• CDR-SB and MMSE data suggest a clinical benefit in patients continuing aducanumab over 48 months (Figure 3).

Cumulative safety data for fixed-dose cohorts
• Cumulative aducanumab safety data for adverse events (AEs) and serious adverse events (SAEs) during the combined placebo-controlled and LTE periods after first exposure to aducanumab are shown in Figure 2.
• Based on incidence reporting by preferred term, the most common AEs (incidence ≥ 15%) were amyloid-related imaging abnormalities (ARIA), headache, fall, urinary tract infection, upper respiratory tract infection and diarrhea.
• The most common SAE (incidence > 5%) was ARIA (n=16 [10.5%]).
• There were a total of 8 deaths: 2 patients received placebo (1 died after leaving the study) and 6 patients received aducanumab.
• The incidence of ARIA-E (ARIA-vasogenic edema) and ARIA-H (ARIA-microhemorrhages, macrohemorrhages, or superficial infarcts) is listed in Table 3.

ARIA characteristics since the start of PRIME in fixed-dose and titration cohorts
• Since the start of the PRIME study:
  • Of the 185 patients dosed with aducanumab, 46 patients experienced ARIA-E.
  • Of those 46 patients, 61% were asymptomatic and 39% had associated symptoms, which were typically mild.
  • ARIA-E tended to occur early in the course of treatment most often within the first 6 months of the first active dose.
  • ARIA events typically resolved or stabilized within 4-12 weeks, with most patients continuing treatment.
  • 8 patients experienced more than one event of ARIA-E.
  • Clinical and imaging characteristics of recurrent ARIA-E were similar to those of ARIA-E previously reported in the PRIME study.

Figure 1. PRIME study design: placebo-controlled and LTE periods

Table 1. Baseline disease characteristics

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=40)</th>
<th>1 mg/kg (n=31)</th>
<th>3 mg/kg (n=32)</th>
<th>6 mg/kg (n=30)</th>
<th>10 mg/kg (n=32)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CDR-SB at baseline</td>
<td>4.6 (1.0)</td>
<td>4.7 (1.0)</td>
<td>4.9 (1.1)</td>
<td>4.9 (1.2)</td>
<td>4.7 (1.1)</td>
</tr>
<tr>
<td>MMSE at baseline</td>
<td>26.5 (7.7)</td>
<td>26.0 (7.6)</td>
<td>24.9 (8.0)</td>
<td>23.9 (8.1)</td>
<td>23.0 (8.0)</td>
</tr>
<tr>
<td>ApoE ε4 carriers</td>
<td>21 (53)</td>
<td>21 (53)</td>
<td>19 (59)</td>
<td>15 (50)</td>
<td>17 (53)</td>
</tr>
</tbody>
</table>

Table 2. Cumulative safety of aducanumab

<table>
<thead>
<tr>
<th></th>
<th>Placebo Switchers1 (n=29)</th>
<th>1 mg/kg Switchers1 (n=31)</th>
<th>3 mg/kg Switchers1 (n=32)</th>
<th>6 mg/kg Switchers1 (n=30)</th>
<th>10 mg/kg Switchers1 (n=32)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number with AE (%)</td>
<td>11 (38)</td>
<td>12 (40)</td>
<td>15 (48)</td>
<td>15 (50)</td>
<td>18 (56)</td>
</tr>
<tr>
<td>Number with SAE (%)</td>
<td>6 (21)</td>
<td>8 (26)</td>
<td>10 (32)</td>
<td>12 (40)</td>
<td>15 (47)</td>
</tr>
<tr>
<td>Number discontinuing treatment due to AE (%)</td>
<td>4 (13)</td>
<td>5 (16)</td>
<td>6 (19)</td>
<td>6 (20)</td>
<td>7 (22)</td>
</tr>
</tbody>
</table>

Table 3. Cumulative ARIA-E incidence for aducanumab

<table>
<thead>
<tr>
<th></th>
<th>Placebo Switchers1 (n=29)</th>
<th>1 mg/kg Switchers1 (n=31)</th>
<th>3 mg/kg Switchers1 (n=32)</th>
<th>6 mg/kg Switchers1 (n=30)</th>
<th>10 mg/kg Switchers1 (n=32)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARIA-E in total</td>
<td>6 (21)</td>
<td>7 (23)</td>
<td>8 (25)</td>
<td>8 (27)</td>
<td>10 (31)</td>
</tr>
<tr>
<td>ARIA-E ε4 carriers</td>
<td>5 (17)</td>
<td>6 (20)</td>
<td>7 (22)</td>
<td>8 (27)</td>
<td>10 (31)</td>
</tr>
<tr>
<td>ARIA-E ε4 non-carriers</td>
<td>1 (3)</td>
<td>1 (3)</td>
<td>1 (3)</td>
<td>1 (3)</td>
<td>2 (6)</td>
</tr>
</tbody>
</table>

Figure 2. Effect of aducanumab on amyloid plaque levels

Figure 3. Effect of aducanumab on clinical decline (exploratory endpoints)