24-Month Analysis of Change From Baseline In Clinical Dementia Rating Scale Cognitive and Functional Domains in PRIME, A Randomized Phase 1b Study of the Anti-Amyloid Beta Monoclonal Antibody Aducanumab

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• This study is funded by Biogen\(^a\)
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• GW is an employee of Cytel
• CH and RMN are employees and shareholders of Neurimmune
• Biogen licensed the worldwide rights to aducanumab from Neurimmune Holding AG in 2007 and is responsible for its development and the commercialization
• As of October 22, 2017, Biogen and Eisai are collaborating on the development and commercialization of aducanumab globally

\(^a\)Medical writing support and editing for this presentation was funded by Biogen and was provided by Nucleus Global.
Overview

• Aducanumab is a human monoclonal antibody that binds to both soluble and insoluble aggregated forms of Aβ, including oligomers, protofibrils, and fibrils\(^1\)

• PRIME is an ongoing Phase 1b study assessing the safety, tolerability, PK and PD of aducanumab in patients with prodromal or mild Alzheimer’s disease

• In PRIME, treatment with aducanumab 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 Alzheimer’s disease enrolled in PRIME experienced a sustained delay in the disease progression as measured by exploratory clinical endpoints at 12, 24 and 36 months\(^1\)-\(^3\)

• The primary endpoint in the PRIME LTE is safety/tolerability

• Exploratory endpoints include:
  o Changes in amyloid PET
  o Measures of clinical decline on the CDR-SB and MMSE

• A post hoc analysis was conducted on the fixed-dose and titration cohorts that assessed cognitive and functional domains of the CDR scale over 24 months, including 12 months from the placebo-controlled period and 12 months from the LTE

PRIME Study Design: Placebo-Controlled and LTE Periods

- **Randomization**: 3:1 active: placebo within cohorts, fixed-dose cohorts stratified by ApoE ε4 status
- Patients randomized to placebo in the placebo-controlled period were switched to aducanumab 3 mg/kg or a titration regimen in the LTE ("placebo switchers"). Patients randomized to aducanumab 3, 6, or 10 mg/kg or titration in the placebo-controlled period were assigned to continue in the same dose group in the LTE ("continuers")

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**Placebo-controlled period**

- 1 mg/kg
- 3 mg/kg
- Placebo

**LTE period**

All patients receive aducanumab

- 3 mg/kg
- 3 mg/kg
- Aducanumab 3 mg/kg or titration (3→6 mg/kg)
- 10 mg/kg

**Titration (ApoE ε4 carriers; 1→10 mg/kg)**

- Placebo (ApoE ε4 carriers)

**Aducanumab titration (3→6 mg/kg)**

- 6 mg/kg
- 10 mg/kg

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*Titration denotes 2 doses of 3 mg/kg followed by subsequent doses of 6 mg/kg. \(^\text{b}\)Titration denotes 2 doses of 1 mg/kg, 4 doses of 3 mg/kg, 5 doses of 6 mg/kg followed by subsequent doses of 10 mg/kg. ApoE ε4, Apolipoprotein E ε4; LTE, long-term extension.*
Titration Dosing Regimen

Placebo-controlled period (Months 1-12)

Study week:
0 4 8 12 16 20 24 28 32 36 40 44 48 52

Dose (mg/kg):
1 mg/kg 3 mg/kg 6 mg/kg 10 mg/kg

By Week 24 average expected dose = 2.9 mg/kg

By Week 52 average expected dose = 5.3 mg/kg

LTE period (Months 12-24)

Titration 1→10 mg/kg

10 mg/kg

By Week 110 average expected dose = 7.6 mg/kg

Placebo-controlled period
(Months 1-12)

By Week 52 average expected dose = 5.3 mg/kg

Placebo

(Months 12-24)

By Week 110 average expected dose = 7.6 mg/kg
Timeline of PET and Clinical Assessments in PRIME

IV infusions every 4 weeks for 52 weeks (14 total) active or placebo

IV infusions every 4 weeks for up to 6 years All patients received active treatment

Screening

Placebo controlled period

LTE (Year 1)

LTE (Year 2)

LTE Years 3-6

Week

Amyloid PET

Clinical Tests

PET, positron emission tomography.
Patient Disposition at 24 Months

Analysis of data up to Month 24. AE, adverse event; LTE, long-term extension.
## Baseline Disease Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=48)</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>
<th>Titration (n=23)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age in years, mean ± SD</strong></td>
<td>73.3 ± 6.8</td>
<td>72.6 ± 7.8</td>
<td>70.5 ± 8.2</td>
<td>73.3 ± 9.3</td>
<td>73.7 ± 8.3</td>
<td>73.1 ± 7.8</td>
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<tr>
<td><strong>ApoE ε4, n (%)</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Carriers</td>
<td>34 (71)</td>
<td>19 (61)</td>
<td>21 (66)</td>
<td>21 (70)</td>
<td>20 (63)</td>
<td>23 (100)</td>
</tr>
<tr>
<td>Non-carriers</td>
<td>14 (29)</td>
<td>12 (39)</td>
<td>11 (34)</td>
<td>9 (30)</td>
<td>12 (38)</td>
<td>0</td>
</tr>
<tr>
<td><strong>Clinical stage, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prodromal</td>
<td>22 (46)</td>
<td>10 (32)</td>
<td>14 (44)</td>
<td>12 (40)</td>
<td>13 (41)</td>
<td>13 (57)</td>
</tr>
<tr>
<td>Mild</td>
<td>26 (54)</td>
<td>21 (68)</td>
<td>18 (56)</td>
<td>18 (60)</td>
<td>19 (59)</td>
<td>10 (43)</td>
</tr>
<tr>
<td><strong>MMSE, mean ± SD</strong></td>
<td>24.7 ± 3.6</td>
<td>23.6 ± 3.3</td>
<td>23.2 ± 4.2</td>
<td>24.4 ± 2.9</td>
<td>24.8 ± 3.1</td>
<td>24.7 ± 3.0</td>
</tr>
<tr>
<td><strong>CDR Global Score, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.5</td>
<td>40 (83)</td>
<td>22 (71)</td>
<td>22 (69)</td>
<td>25 (83)</td>
<td>24 (75)</td>
<td>18 (78)</td>
</tr>
<tr>
<td>1</td>
<td>8 (17)</td>
<td>9 (29)</td>
<td>10 (31)</td>
<td>5 (17)</td>
<td>8 (25)</td>
<td>5 (22)</td>
</tr>
<tr>
<td><strong>CDR-SB, mean ± SD</strong></td>
<td>2.69 ± 1.54</td>
<td>3.40 ± 1.76</td>
<td>3.50 ± 2.06</td>
<td>3.32 ± 1.54</td>
<td>3.14 ± 1.71</td>
<td>3.24 ± 1.84</td>
</tr>
<tr>
<td><strong>PET SUVR, mean composite</strong></td>
<td>1.435</td>
<td>1.441</td>
<td>1.464</td>
<td>1.429</td>
<td>1.441</td>
<td>1.325</td>
</tr>
<tr>
<td><strong>AD medications used,a n (%)</strong></td>
<td>32 (67)</td>
<td>21 (68)</td>
<td>28 (88)</td>
<td>20 (67)</td>
<td>17 (53)</td>
<td>12 (52)</td>
</tr>
</tbody>
</table>

*aCholinesterase inhibitors and/or memantine.
AD, Alzheimer’s disease; ApoE ε4, Apolipoprotein E ε4; CDR-SB, Clinical Dementia Rating–Sum of Boxes; MMSE, Mini-Mental State Examination; PET, positron emission tomography; SD, standard deviation; SUVR, standardized uptake value ratio.
Summary of Previously Presented PRIME 24-Month Interim Results

**Clinical effect of aducanumab (exploratory endpoints)**

- Of the 185 patients dosed with aducanumab since the start of the PRIME study, 46 patients experienced ARIA-E.
- Of the 46 patients who experienced ARIA-E, 65% were asymptomatic and 35% were symptomatic; the majority of symptomatic cases experienced symptoms that were mild to moderate in severity.
- 6 patients experienced more than one episode of ARIA.
- The majority of ARIA events occurred early in the course of treatment; they were typically mild, asymptomatic, and resolved or stabilized within 4-12 weeks, with most patients continuing treatment.

**Amyloid plaque reduction with aducanumab**

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- Of the 46 patients who experienced ARIA-E, 65% were asymptomatic and 35% were symptomatic; the majority of symptomatic cases experienced symptoms that were mild to moderate in severity.
- 6 patients experienced more than one episode of ARIA.
- The majority of ARIA events occurred early in the course of treatment; they were typically mild, asymptomatic, and resolved or stabilized within 4-12 weeks, with most patients continuing treatment.

**Safety (primary endpoint)**

- Of the 185 patients dosed with aducanumab since the start of the PRIME study, 46 patients experienced ARIA-E.
- Of the 46 patients who experienced ARIA-E, 65% were asymptomatic and 35% were symptomatic; the majority of symptomatic cases experienced symptoms that were mild to moderate in severity.
- 6 patients experienced more than one episode of ARIA.
- The majority of ARIA events occurred early in the course of treatment; they were typically mild, asymptomatic, and resolved or stabilized within 4-12 weeks, with most patients continuing treatment.

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*Placebo switchers received aducanumab 3 mg/kg or titration (3 mg/kg → 6 mg/kg or 1 mg/kg → 10 mg/kg) in the LTE. Nominal * P < 0.05; Nominal ** P < 0.01; Nominal *** P < 0.001 vs placebo in the placebo-controlled period and vs placebo switchers in the LTE period. MMSE and CDR-SB are exploratory endpoints. Results based on MMRM, fitted with change from baseline as a dependent variable, and included fixed effects for categorical treatment, categorical visit and treatment-by-visit interaction, continuous baseline value, and laboratory ApoE ε4 status (carrier and non-carrier). ARIA-E, amyloid-related imaging abnormalities - vasogenic edema; CDR-SB, Clinical Dementia Rating–Sum of Boxes; LTE, long-term extension; MMRM, mixed model for repeated measures; MMSE, Mini Mental State Exam; SE, standard error.
The CDR-SB is a validated global assessment of Alzheimer’s disease disability that is capable of tracking the progression of Alzheimer’s disease in the MCI and mild Alzheimer’s disease population.

It assesses a patient’s level of impairment on 6 domains using semi-structured interviews by a trained clinician/rater with the patient and an informant.

Each impairment level of the cognitive and functional domains (except for Personal Care) is rated on a continuum of five levels, with a scale of 0 to 3:

- The five levels of impairment are 0 (none), 0.5 (questionable), 1 (mild), 2 (moderate), and 3 (severe)
- Personal Care uses only 4 levels: 0, 1, 2, and 3
### Baseline CDR Global and Domain Scores

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=48)</th>
<th>Aducanumab</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>1 mg/kg (n=31)</td>
</tr>
<tr>
<td>CDR-SB, mean ± SD</td>
<td>2.69 ± 1.54</td>
<td>3.40 ± 1.76</td>
</tr>
<tr>
<td>CDR cognitive domain score, mean ± SD</td>
<td>1.79 ± 0.87</td>
<td>2.00 ± 0.94</td>
</tr>
<tr>
<td>CDR functional domain score, mean ± SD</td>
<td>0.90 ± 0.83</td>
<td>1.40 ± 1.09</td>
</tr>
</tbody>
</table>

CDR-SB, Clinical Dementia Rating–Sum of Boxes; SD, standard deviation.
Week 54: Effect of Aducanumab on Both CDR Cognitive and Functional Domains

Results based on MMRM, fitted with change from baseline as a dependent variable, and included fixed effects for categorical treatment, categorical visit and treatment-by-visit interaction, continuous baseline value, and laboratory ApoE ε4 status (carrier and non-carrier). CDR, Clinical Dementia Rating; CI, confidence interval; MMRM, mixed model for repeated measures.
**Week 110: Effect of Aducanumab on Both CDR Cognitive and Functional Domains**

**CDR Cognitive Domain (Week 110)**

**Aducanumab dose**

- 1 → 3 mg/kg (n=14)
- 3 mg/kg (n=16)
- 6 mg/kg (n=23)
- 10 mg/kg (n=15)
- Titration (n=16)

Favors aducanumab vs placebo switchers

**CDR Functional Domain (Week 110)**

**Aducanumab dose**

- 1 → 3 mg/kg (n=14)
- 3 mg/kg (n=16)
- 6 mg/kg (n=23)
- 10 mg/kg (n=15)
- Titration (n=16)

Favors aducanumab vs placebo switchers

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\(^a\)Placebo switchers received aducanumab 3 mg/kg or titration (3 mg/kg → 6 mg/kg or 1 mg/kg → 10 mg/kg) in the LTE. Results based on MMRM, fitted with change from baseline as a dependent variable, and included fixed effects for categorical treatment, categorical visit and treatment-by-visit interaction, continuous baseline value, and laboratory ApoE ε4 status (carrier and non-carrier). CDR, Clinical Dementia Rating; CI, confidence interval; MMRM, mixed model for repeated measures.
Summary

• Analyses of exploratory clinical endpoint CDR-SB suggest a continued benefit on the rate of clinical decline over 24 months
• Post hoc analysis suggests a beneficial effect of aducanumab on progression of both cognitive and functional CDR domain scores over 24 months
• These data continue to support further investigation of the clinical efficacy and safety of aducanumab in patients with early Alzheimer’s disease in the ENGAGE and EMERGE Phase 3 trials
Acknowledgments

We thank all the patients and their family members participating in the aducanumab studies, as well as the investigators and their staff conducting these studies.