Aducanumab Titration Dosing Regimen: 36-month Analyses from PRIME, a Phase 1b Study in Patients with Early Alzheimer’s Disease

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CTAD 2018, Barcelona, Spain

October 26, 2018
Disclosures

• This study is funded by Biogen\textsuperscript{a}
• SBH, CCV, TC, JO, RR, DP, PvR, SC, LS, CP and AS are employees and shareholders of Biogen
• 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

\textsuperscript{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\textsuperscript{1,2}
- PRIME is an ongoing Phase 1b study assessing the safety, tolerability, pharmacokinetics and pharmacodynamics of aducanumab in patients with prodromal or mild Alzheimer’s disease\textsuperscript{1}
- Here, we report 36-month data for both fixed-dose and titration cohorts
- The primary endpoint in PRIME is safety/tolerability
- Exploratory endpoints in the LTE include:
  - Changes in amyloid PET
  - Measures of clinical decline such as the CDR-SB and MMSE

CDR-SB, Clinical Dementia Rating-Sum of Boxes; MMSE, Mini-Mental State Examination; PET, positron emission tomography; LTE, long-term extension.
**PRIME Study Design**

**Placebo-controlled period**
- 1 mg/kg
- 3 mg/kg
- 10 mg/kg
- Placebo
- 6 mg/kg
- Placebo
- *Titration (ApoE ε4 carriers; 1→10 mg/kg)*
  - Placebo (ApoE ε4 carriers)

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

**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*).

*Titration denotes 2 doses of 3 mg/kg followed by subsequent doses of 6 mg/kg. *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

Placebo

LTE period (Months 12-24)

Titration 1→10 mg/kg

By Week 24 average expected dose = 2.9 mg/kg

By Week 52 average expected dose = 5.3 mg/kg

By Week 110 average expected dose = 7.6 mg/kg

LTE period (Months 24-36)

10 mg/kg

By Week 166 average expected dose = 8.4 mg/kg
Patient Disposition at 36 Months

Dosed in placebo-controlled period
- Pooled placebo: 48
- 1 mg/kg: 31
- 3 mg/kg: 32
- 6 mg/kg: 30
- 10 mg/kg: 32
- Titration: 23

Completed treatment in the placebo-controlled period
- 197 randomized (196 dosed)
- Discontinued treatment in the first two years of LTE
  - Adverse event: 8
  - Disease progression: 1
  - Consent withdrawn: 1
  - Death: 0
  - Other: 1

Switchers
- 37
- Discontinued treatment in the first two years of LTE
- Total: 18

Continuers
- 152
- Discontinued treatment in the first two years of LTE
- Total: 18

Completed treatment at 36-months
- 98
- Discontinued treatment in the first two years of LTE
- Total: 18

Analysis of data up to Month 36. 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>
</tr>
<tr>
<td><strong>ApoE ε4, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</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, 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.*
PET Amyloid Imaging
**Effect of Aducanumab on Amyloid Plaque Levels (Composite SUVR)**

<table>
<thead>
<tr>
<th>Aducanumab</th>
<th>Analysis visit (weeks)</th>
<th>Placebo-controlled period</th>
<th>LTE period (all patients received aducanumab)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0 26 54 110 166</td>
<td>Placebo n=42 42 38</td>
<td>Placebo n=42 42 38</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Placebo switchers 26 22</td>
<td>Placebo switchers 26 22</td>
</tr>
<tr>
<td>1 mg/kg</td>
<td></td>
<td>1 mg/kg n=26 26 21</td>
<td>1 mg/kg n=26 26 21</td>
</tr>
<tr>
<td>3 mg/kg</td>
<td></td>
<td>3 mg/kg n=29 27 26</td>
<td>3 mg/kg n=29 27 26</td>
</tr>
<tr>
<td>6 mg/kg</td>
<td></td>
<td>6 mg/kg n=24 23 23</td>
<td>6 mg/kg n=24 23 23</td>
</tr>
<tr>
<td>10 mg/kg</td>
<td></td>
<td>10 mg/kg n=28 27 21</td>
<td>10 mg/kg n=28 27 21</td>
</tr>
<tr>
<td>Titration</td>
<td></td>
<td>Titration n=18 17 16</td>
<td>Titration n=18 17 16</td>
</tr>
</tbody>
</table>

**Difference from placebo switchers at Week 166**

<table>
<thead>
<tr>
<th></th>
<th>** P&lt;0.05; ** P&lt;0.01; *** P&lt;0.001 vs PBO in the placebo-controlled period and vs PBO switchers in the LTE period.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo switchers</td>
</tr>
<tr>
<td></td>
<td>Continuers</td>
</tr>
<tr>
<td></td>
<td>0.050</td>
</tr>
<tr>
<td></td>
<td>0.007</td>
</tr>
<tr>
<td></td>
<td>-0.030</td>
</tr>
<tr>
<td></td>
<td>-0.053</td>
</tr>
<tr>
<td></td>
<td>-0.060</td>
</tr>
</tbody>
</table>

* P<0.05; ** P<0.01; *** P<0.001 vs PBO in the placebo-controlled period and vs PBO switchers in the LTE period. *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). LTE, long-term extension; MMRM, mixed model for repeated measures; PBO, placebo; SE, standard error.
Effect of Aducanumab on Amyloid Plaque Levels (Centiloid Scale)

Adjusted mean change from baseline (±SE)

Weeks 0 26 54 110 166
Placebo n=42 42 38 PBO switchers a 26 22
1 mg kg n=26 26 21 3 mg/kg 13 6
3 mg/kg n=29 27 26 18 12
6 mg/kg n=24 23 23 18 15
10 mg/kg n=28 27 21 13 7
Titration n=18 17 16

Placebo switchers
Continuers

Change from baseline at Week 166
-43.72
-53.16
-64.71
-61.32
-66.33
-67.87

* P<0.05; ** P<0.01; *** P<0.001 vs PBO in the placebo-controlled period and vs PBO switchers in the LTE period. *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). The centiloid conversion equation for amyloid PET SUVR composite score (RR = whole cerebellum) is 100*(SUVR-1.0034)/0.4536. LTE, long-term extension; MMRM, mixed model for repeated measures; PBO, placebo; SE, standard error.
Effect of Aducanumab on Amyloid Plaque Levels (Mean SUVR)

The value of 1.10 has been proposed as a quantitative cut-point suggested to discriminate between a positive and negative scan.\(^1\)

Clinical Endpoints
Effect of Aducanumab on Clinical Decline as Measured by CDR-SB (Exploratory Endpoint)

Aducanumab Difference from placebo switchers at Week 166:

- Placebo switchers: 1.38
- 1 mg/kg: -0.33
- 3 mg/kg: -0.97
- 6 mg/kg: -1.72
- 10 mg/kg: -1.95

Details:

- 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. CDR-SB is an exploratory endpoint. 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-SB: Clinical Dementia Rating–Sum of Boxes; LTE: long-term extension; MMRM, mixed model for repeated measures; PBO, placebo; SE, standard error.
Effect of Aducanumab on Clinical Decline as Measured by MMSE (Exploratory Endpoint)

**Placebo-controlled period**

- **LTE period**
  - (all patients received aducanumab)

### Results

- **Placebo-controlled period**
  - **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.

### Analysis

- **Adjusted mean change from baseline (±SE)**
- **Weeks**
  - 0, 24, 52, 76, 108, 132, 164

### Data

- **Placebo**
  - n=45, 44, 40
- **PBO switchers**
  - n=31, 29, 25, 24
- **1 mg kg**
  - n=26, 26, 25
- **3 mg/kg**
  - n=29, 29, 26
- **6 mg/kg**
  - n=28, 28, 26
- **10 mg/kg**
  - n=30, 29, 25
- **Titration**
  - n=21, 20, 21

### Notes

- *P<0.05 vs placebo in the placebo-controlled period and vs placebo switchers in the LTE period.*
- 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 MMSE is an exploratory endpoint. 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). LTE, long-term extension; MMRM, mixed model for repeated measures; MMSE, Mini-Mental State Examination; PBO, placebo; SE, standard error.

### Figure Legend

- **Difference from placebo switchers at Week 164**
  - Placebo: -2.32
  - 1 mg kg: 0.50
  - 3 mg/kg: 1.76
  - 6 mg/kg: 2.47
  - 10 mg/kg: 2.52

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*P<0.05 vs placebo in the placebo-controlled period and vs placebo switchers in the LTE period. 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 MMSE is an exploratory endpoint. 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). LTE, long-term extension; MMRM, mixed model for repeated measures; MMSE, Mini-Mental State Examination; PBO, placebo; SE, standard error.
Safety and Tolerability
Cumulative Aducanumab Safety  
*(Events After First Aducanumab Exposure)*

<table>
<thead>
<tr>
<th></th>
<th>Placebo Switchers&lt;sup&gt;a&lt;/sup&gt;</th>
<th>1 mg/kg → 3 mg/kg (n=31)</th>
<th>Continuers&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=37)</td>
<td></td>
<td>3 mg/kg (n=32)</td>
</tr>
<tr>
<td>Number with an AE (%)</td>
<td>37 (100)</td>
<td>29 (94)</td>
<td>30 (100)</td>
</tr>
<tr>
<td>Number with an SAE (%)</td>
<td>21 (57)</td>
<td>11 (35)</td>
<td>14 (47)</td>
</tr>
<tr>
<td>Number discontinuing treatment due to AE (%)</td>
<td>11 (30)</td>
<td>4 (13)</td>
<td>4 (13)</td>
</tr>
</tbody>
</table>

<sup>a</sup>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. <sup>b</sup>Patients who were randomized to receive 3, 6, and 10 mg/kg were scheduled to receive the same dose throughout the LTE. Patients who received a dose reduction during the placebo-controlled period due to ARIA were able to titrate up to the planned dose at study start after consenting to the protocol amendment. <sup>c</sup>Based on incidence reporting by preferred term. AE, adverse event; ARIA, amyloid-related imaging abnormality; LTE, long-term extension; SAE, serious AE.

- The most common AEs (incidence ≥ 15%) by preferred term were ARIA, headache, fall, urinary tract infection, diarrhea, nasopharyngitis, and upper respiratory tract infection
- The most common SAE (incidence ≥ 5%) by preferred term was ARIA (n=17 [9%])

There were a total of 6 deaths reported in patients who were treated with aducanumab; an additional 2 deaths occurred in patients receiving placebo (1 patient died after leaving the study)
## Cumulative Incidence of ARIA  
*(Events After First Aducanumab Exposure)*

<table>
<thead>
<tr>
<th></th>
<th>Placebo Switchers&lt;sup&gt;c&lt;/sup&gt;</th>
<th>1 mg/kg → 3 mg/kg</th>
<th>Continuers&lt;sup&gt;d&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>3 mg/kg</td>
</tr>
<tr>
<td>Patients with at least 1 post-baseline MRI</td>
<td>37</td>
<td>31</td>
<td>32</td>
</tr>
<tr>
<td>ARIA-E&lt;sup&gt;a&lt;/sup&gt;, n/total (%)</td>
<td>8/37 (22)</td>
<td>4/31 (13)</td>
<td>2/32 (6)</td>
</tr>
<tr>
<td>ApoE ε4 carriers</td>
<td>7/25 (28)</td>
<td>4/19 (21)</td>
<td>1/21 (5)</td>
</tr>
<tr>
<td>ApoE ε4 non-carriers</td>
<td>1/12 (8)</td>
<td>0/12 (0)</td>
<td>1/11 (9)</td>
</tr>
<tr>
<td>Discontinued treatment,&lt;sup&gt;b&lt;/sup&gt; n (%)</td>
<td>5 (14)</td>
<td>1 (3)</td>
<td>-</td>
</tr>
<tr>
<td>Isolated ARIA-H, n (%)</td>
<td>2 (5)</td>
<td>1 (3)</td>
<td>7 (22)</td>
</tr>
</tbody>
</table>

<sup>a</sup>ARIA-E with or without ARIA-H.  
<sup>b</sup>ARIA-E and either 1) no doses after onset of ARIA-E or 2) have subsequent discontinuation due to ARIA.  
<sup>c</sup>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.  
<sup>d</sup>Patients who were randomized to receive 3, 6, and 10 mg/kg were scheduled to receive the same dose throughout the LTE. Patients who received a dose reduction during the placebo-controlled period due to ARIA were able to titrate up to the planned dose at study start after consenting to the protocol amendment.

ARIA-E, ARIA-vasogenic edema; ARIA-H, ARIA-microhemorrhages, macrohemorrhages, or superficial siderosis; MRI, magnetic resonance imaging.
Overall ARIA Characteristics (All Cohorts)

- Since the start of the PRIME study:
  - Of the 185 patients dosed with aducanumab, 46 patients experienced ARIA-E with a cumulative incidence of 25% over the course of the study
    - Of the 46 patients with ARIA-E, 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
Summary

• Amyloid plaque levels continued to decrease in a dose- and time-dependent manner in patients treated with aducanumab from the titration and fixed-dose cohorts who completed the second year of the LTE
  - Mean amyloid plaque levels in both the 10 mg/kg fixed-dose and titration cohorts reached and remained at an SUVR level below 1.1, which has been proposed as a quantitative cut-point suggested to discriminate between a positive and negative scan1
• Analyses of exploratory clinical endpoints CDR-SB and MMSE suggest a continued benefit on the rate of clinical decline over 36 months
  - Clinical effects with titrated aducanumab in the second year of the LTE were generally consistent with findings in the 10 mg/kg fixed-dose treatment group
• 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 AD 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.