What have we learned from aducanumab?

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Disclaimer

• Aducanumab, is an investigational medicine and the benefit/risk profile has not been fully established. It has not received any marketing authorization and there is no guarantee that it will obtain such authorization in the future.

• The information and any data presented is early interim data from ongoing clinical trials and it is made available for scientific discussion only, in consideration of the general interest of the scientific community with respect to any progress in the research and development of possible treatments for Alzheimer disease.

• The information and any data presented are developed from scientific research and are not intended to predict the availability of any particular drug or therapy.
Accumulation of Aβ is a core pathology in Alzheimer’s disease (AD)
Our understanding of the amyloid pathway today

- The relevant pathological form of Aβ remains elusive
- Soluble oligomers &/or insoluble fibrils may play important roles in disease

Profiles of amyloid-targeted immunotherapies

<table>
<thead>
<tr>
<th></th>
<th>Aducanumab</th>
<th>BAN2401</th>
<th>Gantenerumab</th>
<th>Crenezumab</th>
<th>MEDI-1814</th>
<th>LY3002813</th>
<th>Bapineuzumab</th>
<th>Solanezumab</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Current Status</strong></td>
<td>Phase 3</td>
<td>Phase 2</td>
<td>Phase 3</td>
<td>Phase 3</td>
<td>Phase 2</td>
<td>Discontinued</td>
<td>Partially halted</td>
<td></td>
</tr>
<tr>
<td><strong>Origin</strong></td>
<td>Human (RTM)</td>
<td>Humanized</td>
<td>Human (RTM)</td>
<td>Humanized</td>
<td>Humanized</td>
<td>Humanized</td>
<td>Humanized</td>
<td></td>
</tr>
<tr>
<td><strong>Target</strong></td>
<td>Fibrillar and Oligomeric Aβ</td>
<td>Fibrillar and Oligomeric Aβ</td>
<td>Fibrillar and Oligomeric Aβ</td>
<td>All forms of Aβ: Oligomeric, Fibrillar, Monomeric</td>
<td>Soluble monomeric Aβ(1-42)</td>
<td>N3pG</td>
<td>All forms of Aβ: Fibrillar, Oligomeric, Monomeric</td>
<td>Soluble monomeric Aβ</td>
</tr>
<tr>
<td><strong>Epitope</strong></td>
<td>N-terminus (3-7)</td>
<td>N-terminus (1-16)</td>
<td>Nt (3-11) + mid (18-27)</td>
<td>Mid-domain (13-24)</td>
<td>C-terminus (X-42)</td>
<td>Aβp3-x</td>
<td>N-terminus (1-5)</td>
<td>Mid-domain (16-26)</td>
</tr>
<tr>
<td><strong>Effector Function</strong></td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Reduced</td>
<td>Reduced</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Plaque/CA A binding</strong></td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Low</td>
<td>?</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td><strong>ARIA</strong></td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

RTM, reverse translational medicine; BACEi, β-site APP-cleaving enzyme inhibitor; N3pG, pyroglutamate amyloid beta.

What we have learned about the molecular characteristics of aducanumab
Aducanumab is a human IgG1 anti-Aβ monoclonal antibody developed in partnership with Neurimmune.

CMC, chemistry and manufacturing controls; IgG, immunoglobulin G; Tox, toxicology.
Aducanumab targets the N-terminus of Aβ

Aβ amino acid sequence

1DAEFRHDSGYEVHHQKLVFFAEDVGSNKGAIIGLMVGGVIA42

Aβ binding Specificity
- All forms of Aβ
- Aggregated Aβ
- Soluble Aβ

*Denotes development that has been discontinued or partially halted.
Structure of aducanumab Fab with Aβ1-11 shows minimal conformational change in Fab upon peptide binding

(2.1 Å) of aducanumab Fab with Aβ1-11

- Residues 2-7 adopt an extended conformation
- Key interactions with CDRs H2, H3, L3

CDRs, complementary-determining regions.
Aducanumab is highly selective for Aβ aggregates

**Negative Stain Electron Microscopy**

- Antibody associated with fibrils

**Dot Blot**

- Binding of immunogold-labeled aducanumab
- Binding to insoluble fibrillar and soluble oligomeric Aβ1-40

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Aducanumab does not bind to soluble monomeric Aβ

- Biochemical assays demonstrate:
  - High affinity binding of BIIB037 for aggregated Aβ (EC₅₀ ≈ 0.2nM)
  - No binding of BIIB037 to soluble monomeric Aβ (EC₅₀ > 1000nM)

EC₅₀, half maximal effective concentration.
Aducanumab binding epitope may determine selective binding to Aβ aggregates

- A shallow and compact epitope may contribute to the selectivity for high molecular weight Aβ forms, without targeting Aβ monomers.

### Buried Surface Area and Contacts

<table>
<thead>
<tr>
<th>Protein</th>
<th>Buried Surface Area (Å²)</th>
<th>Contacts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aducanumab</td>
<td>506</td>
<td>12</td>
</tr>
<tr>
<td>BAN2401</td>
<td>610</td>
<td>18</td>
</tr>
<tr>
<td>PFA1</td>
<td>670</td>
<td>20</td>
</tr>
<tr>
<td>Bapineuzumab</td>
<td>565</td>
<td>23</td>
</tr>
<tr>
<td>Gantenerumab</td>
<td>903</td>
<td>24</td>
</tr>
</tbody>
</table>

BSA, buried surface area; CDRs, complementary-determining regions.
Aducanumab achieves sufficient brain exposure to bind amyloid deposits in APP transgenic mice (Tg2576)

**In vivo binding of aducanumab to amyloid deposits**
Visualized with anti-human IHC

**Pattern of amyloid deposition**
Serial section visualized with pan-Aβ IHC

APP, amyloid precursor protein; IHC, immunohistochemistry.
6-month aducanumab dosing reduces amyloid plaque in a dose-dependent manner in transgenic mice (Tg2576)

**DEA Fraction**

Guanidine Fraction

PBS 0.3 1 3 10 30

% of control

Cortex

DEA Fraction

Hippocampus

Dose (mg/kg)

% control

Aβ40

Aβ42

6E10

ThioS

Dose (mg/kg)

% control

-50%

*P<0.05 versus control.

Aducanumab restores neurite calcium levels in transgenic mice with amyloid plaques
Aducanumab recruits microglial cells and induces phagocytosis-mediated clearance of amyloid plaques in Tg2576 mice.

PBS, phosphate buffered saline; Iba-1, ionizing calcium-binding adaptor molecule 1.
Clinical learnings from the Phase 1b PRIME study
Aducanumab Phase 1b study (PRIME) design

- 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 dementia.
- 197 subjects randomized, 196 dosed; 12-month placebo-controlled period, ongoing LTE.

<table>
<thead>
<tr>
<th>Population</th>
<th>Treatment Arms</th>
<th>Endpoints</th>
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</thead>
<tbody>
<tr>
<td>• Prodromal/MCI due to AD mild AD dementia</td>
<td>Placebo* (n=48)</td>
<td>• Primary endpoint: safety &amp; tolerability</td>
</tr>
<tr>
<td>• MMSE ≥20</td>
<td>1 mg/kg (n=31)</td>
<td>• Secondary endpoints: serum PK, immunogenicity, change in amyloid PET (Week 26)</td>
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<tr>
<td>• Stable concomitant medications</td>
<td>3 mg/kg (n=31)</td>
<td>• Exploratory endpoints included CDR–SB, MMSE, change in amyloid PET (Week 54); in the LTE all endpoints except safety were exploratory</td>
</tr>
<tr>
<td>• Positive amyloid PET</td>
<td>6 mg/kg (n=30)</td>
<td></td>
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<tr>
<td></td>
<td>10 mg/kg (n=32)</td>
<td></td>
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<tr>
<td></td>
<td>Titrator ApoE ε4 carriers; 1—10 mg/kg (n=23)</td>
<td></td>
</tr>
</tbody>
</table>

- **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 continued in the same dose group in the LTE ("continuers").

PK, pharmacokinetics; PD, pharmacodynamics; LTE, long-term extension; MCI, mild cognitive impairment; MMSE, Mini–Mental State Examination; PET, positron-emission tomography; CDR-SB, Clinical Dementia Rating-Sum of Boxes.

Target engagement
Amyloid plaque reduction as a measure of target engagement

- Amyloid PET when the PRIME study started was a very new technology for multicenter clinical trials
- Two pioneering studies bapineuzumab ($^{11}$C-PiB PET) and gantenerumab moved the fields understanding on
  - Sample sizes
  - Placebo response
  - Analysis methodologies
- Aducanumab PRIME study
  - Screened all subjects for baseline levels of amyloid
  - >20 clinical sites
  - $^{18}$F-AV-45 (Amyvid)
  - Larger sample sizes per arm

$^{11}$C-PiB PET, Pittsburgh compound B positron-emission tomography.
*Difference between patients in the placebo group and those in the bapineuzumab group at week 78= -0.24 (p=0.003).
Aducanumab target engagement: dose- and time-dependent reduction in amyloid plaque as measured by PET

Dose and time dependent reduction in composite SUVR (PET)\(^1\)

- Statistically significant reduction in amyloid plaque seen as early as 6 months
- No increase in placebo arms

Amyloid-β (Aβ) plaque reduction: example amyloid PET images\(^2\)

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\(^1\) ANCOVA, analysis of covariance; PET, positron-emission tomography; SE, standard error; SUVR, standard uptake value ratio.

\(^2\) Nominal \(p\) values: * \(P<0.05\); ** \(P<0.01\); *** \(P<0.001\) vs placebo. Analyses based on observed data. ANCOVA for change from baseline with factors of treatment, laboratory ApoE ε4 status (carrier and non-carrier), and baseline composite SUVR. PD analysis population is defined as all randomized patients who received at least 1 dose of study medication and had at least 1 post-baseline assessment of the parameter.

1. Viglietta et al. Aducanumab titration dosing regimen: 12-month interim analysis from PRIME, a randomized, double-blind, placebo-controlled Phase 1b study in patients with prodromal or mild Alzheimer’s disease. Presented at the 9th edition of Clinical Trials on Alzheimer’s Disease (CTAD), December 8‒10, 2016, San Diego, CA, USA.
Aducanumab target engagement: dose- and time-dependent reduction in amyloid plaque in SUVR and centiloid

**Change in SUVR**

**Change in centiloid**

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**Standardization:**
- Centiloid facilitates cross ligand / cross trial comparison
Dose- and time-dependent reductions in SUVR observed with aducanumab regardless of reference/target regions

Aducanumab reduces amyloid plaque in regions anticipated to have amyloid

Effect size for each brain target region in 10 mg/kg aducanumab group by reference region at week 54

SUVR, standard uptake value ratio.
P<0.05; **P<0.01; ***P<0.001 vs placebo. Analyses based on observed data. ANCOVA for change from baseline with factors of treatment, laboratory ApoE ε4 status (carrier and non-carrier), and baseline composite SUVR. PD analysis population is defined as all randomized patients who received at least 1 dose of study medication and had at least 1 post-baseline assessment of the parameter.

Aducanumab reduction in amyloid plaque is equivalent across prodromal/MCI due to AD and Mild AD dementia
Aducanumab reduction in amyloid plaque is equivalent in ApoE ε4 carriers and non-carriers

<table>
<thead>
<tr>
<th>Carrier</th>
<th>Non-carrier</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adjusted mean change ± SE</strong></td>
<td></td>
</tr>
</tbody>
</table>

- **Weeks** 54
  - **Placebo** 11
  - **1 mg kg** 9
  - **3 mg/kg** 9
  - **6 mg/kg** 6
  - **10 mg/kg** 7
  - **Titration** -

**ANCOVA**, analysis of covariance; SE, standard error.
Analysis based on ANCOVA model with factors of treatment and baseline.
Data on file.
Aducanumab continues to reduce amyloid plaque levels over 48 Months – by up to 75 centiloid units

LTE, long-term extension; MMRM, mixed model for repeated measures; PBO, placebo; SE, standard error, SUVR, standard uptake value ratio.

* P<0.05; ** P<0.01; *** P<0.001 vs PBO in the placebo-controlled period and vs PBO switchers in the LTE period.

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). Data on file.
Aducanumab reduction in amyloid plaque falls below a purported SUVR cut point for positive pathology

The value of 1.10 is a purported quantitative cut-point that discriminates between positive and negative scans.¹
Clinical endpoints
(Exploratory endpoints in Phase 1b study)
Clinical proof of concept: effect of aducanumab on clinical decline as measured by CDR-SB & MMSE

**Change in CDR-SB**

- **Weeks 0, 26, 54**
  - Placebo: n=44, 44, 39
  - 1 mg/kg: n=38, 26, 23
  - 3 mg/kg: n=39, 39, 27
  - 6 mg/kg: n=36, 34, 26
  - 10 mg/kg: n=36, 26, 23
  - Titration: n=22, 22, 21

**Change in MMSE**

- **Weeks 0, 24, 52**
  - Placebo: n=45, 44, 45
  - 1 mg/kg: n=30, 29, 25
  - 3 mg/kg: n=29, 29, 25
  - 6 mg/kg: n=23, 23, 25
  - 10 mg/kg: n=30, 29, 25
  - Titration: n=21, 22, 21

**CDR-SB** is an exploratory endpoint. Analyses based on observed data. ANCOVA for change from baseline with factors of treatment, laboratory ApoE ε4 status (carrier and non-carrier), and baseline CDR-SB. Efficacy analysis population is defined as all randomized subjects who received at least 1 dose of study medication and had at least 1 post-baseline questionnaire assessment.

**MMSE** is an exploratory endpoint. Analyses based on observed data. ANCOVA for change from baseline with factors of treatment, laboratory ApoE ε4 status (carrier and non-carrier), and baseline MMSE. Efficacy analysis population is defined as all randomized patients who received at least 1 dose of study medication and had at least 1 post-baseline questionnaire assessment.

MRRM, mixed model for repeated measures. CDR-SB, Clinical Dementia Rating-Sum of Boxes; LTE, long-term extension; PBO, placebo; SE, standard error.

Vigilietta et al. Aducanumab titration dosing regimen: 12-month interim analysis from PRIME, a randomized, double-blind, placebo-controlled Phase 1b study in patients with prodromal or mild Alzheimer’s disease. Presented at the 9th edition of Clinical Trials on Alzheimer’s Disease (CTAD), December 8–10, 2016, San Diego, CA, USA.
Clinical stage impacts disease progression in the placebo arms but does not impact treatment effect of aducanumab.

MMSE, Mini–Mental State Examination; CDR-SB, Clinical Dementia Rating-Sum of Boxes; SE, standard error; ANCOVA, analysis of covariance. Analysis based on ANCOVA model with factors of treatment, ApoE ε4 status (carrier/non-carrier) and baseline. Data on file.
ApoE ε4 status does not impact disease progression or treatment effect with Aducanumab on CDR-SB and MMSE.

**CDR-SB**

- **Carrier**
  - Weeks 54
    - Placebo 28
    - 1 mg/kg 13
    - 3 mg/kg 18
    - 6 mg/kg 19
    - 10 mg/kg 16
    - Titration 21

- **Non-carrier**
  - Weeks 54
    - Placebo 11
    - 1 mg/kg 10
    - 3 mg/kg 9
    - 6 mg/kg 7
    - 10 mg/kg 7
    - Titration -

**MMSE**

- **Carrier**
  - Weeks 52
    - Placebo 28
    - 1 mg/kg 15
    - 3 mg/kg 17
    - 6 mg/kg 19
    - 10 mg/kg 16
    - Titrations 21

- **Non-carrier**
  - Weeks 52
    - Placebo 12
    - 1 mg/kg 10
    - 3 mg/kg 9
    - 6 mg/kg 7
    - 10 mg/kg 9
    - Titrations -

**Notes:**

- MMSE, Mini–Mental State Examination; CDR-SB, Clinical Dementia Rating-Sum of Boxes; SE, standard error; ANCOVA, analysis of covariance.
- Analysis based on ANCOVA model with factors of treatment, ApoE E4 status (carrier/non-carrier) and baseline.
- Data on file.
PRIME: Treatment up to 48 months CDR–SB & MMSE data suggests clinical benefit in patients continuing aducanumab

**Change in CDR-SB**

<table>
<thead>
<tr>
<th>Placebo-controlled period</th>
<th>LTE period (all patients received aducanumab)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Analysis visit (weeks)</td>
<td>Placebo</td>
</tr>
<tr>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>26</td>
<td>0</td>
</tr>
<tr>
<td>52</td>
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<td>76</td>
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<td>108</td>
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<td>132</td>
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<td>164</td>
<td>0</td>
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<tr>
<td>188</td>
<td>0</td>
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<tr>
<td>220</td>
<td>0</td>
</tr>
</tbody>
</table>

**Change in MMSE**

**Difference from placebo switchers at Week 222**

**Difference from placebo switchers at Week 220**

**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).

**MMRM** mixed model for repeated measures, **CDR-SB**, Clinical Dementia Rating–Sum of Boxes; **LTE**, long-term extension; **PBO**, placebo; **SE**, standard error.

Analysis based on ANCOVA model with factors of treatment, ApoE E4 status (carrier/non-carrier) and baseline.

Data on file.
PRIME: Reduction in brain amyloid correlates with slowing of cognitive decline at the individual and group levels

**At the Individual-subject Level**
Reduction in brain amyloid is significantly correlated with slowing of cognitive decline as measured by CDR-SB in the 10 mg/kg group at Week 54

**Correlation between changes in PET SUVR and CDR-SB at Week 54 adjusting for baseline PET SUVR (a)**

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>Pearson correlation</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>37</td>
<td>-0.03</td>
<td>0.8854</td>
</tr>
<tr>
<td>1 mg/kg</td>
<td>21</td>
<td>0.03</td>
<td>0.9163</td>
</tr>
<tr>
<td>3 mg/kg</td>
<td>26</td>
<td>0.49</td>
<td>0.0119</td>
</tr>
<tr>
<td>6 mg/kg</td>
<td>23</td>
<td>0.24</td>
<td>0.2861</td>
</tr>
<tr>
<td>Titration</td>
<td>16</td>
<td>0.39</td>
<td>0.1485</td>
</tr>
<tr>
<td>10 mg/kg</td>
<td>19</td>
<td>0.64</td>
<td>0.0034</td>
</tr>
</tbody>
</table>

**At the Group (Dose) Level**
Treatment-induced reduction in brain amyloid is correlated with treatment-induced slowing of cognitive decline as measured by CDR-SB at Week 54

Data on file. Analyses based on subjects who had changes from baseline at Week 54 in both amyloid PET SUVR and CDR-SB. Amyloid PET SUVR is calculated using whole cerebellum.

a. The partial correlations that adjusted for the baseline amyloid PET SUVR were presented.
b. Based on ANCOVA for change from baseline in PET SUVR, with factors of treatment, laboratory ApoE ε4 status (carrier and non-carrier) and baseline PET.
c. Based on ANCOVA for change from baseline in CDR-SB, with factors of treatment, laboratory ApoE ε4 status (carrier and non-carrier), baseline CDR-SB, and baseline PET.
What about the 6 mg/kg cohort?

- **PET performs as expected in the 6mg/kg cohort**
- **But 6 mg/kg does not perform as expected on the clinical endpoints – particularly MMSE**
  - We have done an extensive review of the data
    - No detectable differences in baseline characteristics
    - Baseline MMSE and CDR-SB scores not different than other cohorts
    - Placebo decline of 6mg/kg cohort is consistent with other cohorts
    - No detectable enrollment, site/rater differences
      - Majority of data was collected prior to announcement of first results in 1, 3, and 10 mg/kg cohorts.
    - These sample sizes are very small for clinical endpoints; PRIME was not powered to detect clinical effects
    - The inconsistency is either due to chance alone, resulting from the small sample sizes, or caused by unknown or unobserved factors.
    - In the phase 3 study, parallel group design and larger sample size should address similar inconsistencies

### Table 1: Difference from placebo at Week 52

<table>
<thead>
<tr>
<th>MMSE Analysis visit (weeks)</th>
<th>Placebo n= 45, 44, 40</th>
<th>1mg/kg adu n= 26, 26, 25</th>
<th>3mg/kg adu n= 29, 29, 26</th>
<th>6 mg/kg adu n= 28, 28, 26</th>
<th>10 mg/kg adu n= 30, 29, 25</th>
<th>Titration n= 21, 20, 21</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Week 26</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
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<td></td>
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<tr>
<td>1 mg/kg adu</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>3 mg/kg adu</td>
<td></td>
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<tr>
<td>6 mg/kg adu</td>
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<td>Titration</td>
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<tr>
<td><strong>Week 54</strong></td>
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<tr>
<td>Placebo</td>
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<tr>
<td>1 mg/kg adu</td>
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<td>3 mg/kg adu</td>
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<td>10 mg/kg adu</td>
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<tr>
<td>Titration</td>
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</table>

### Figure

**Amyloid plaque reduction by SUVR**

- **Placebo vs others:**
  - Placebo (42)
  - 1 mg/kg adu (21)
  - 3 mg/kg adu (21)
  - 6 mg/kg adu (21)
  - 10 mg/kg adu (21)
  - Titration (21)

**MMSE**

- **Difference from placebo at Week 52**
  - *P<0.05; **P<0.01; ***P<0.001 vs placebo.

** Analysis based on observed data. ANCOVA for change from baseline with factors of treatment, laboratory APoE e4 status (carrier and non-carrier), and baseline CDR-SB. Efficacy analysis population is defined as all randomized subjects who received at least 1 dose of study medication and had at least 1 post-baseline questionnaire assessment. PD analysis population is defined as all randomized subjects who received at least 1 dose of study medication and had at least 1 post-baseline assessment of the parameter. Vigiletta et al. Aducanumab titration dosing regimen. 12-month interim analysis from PRIME, a randomized, double-blind, placebo-controlled Phase 1b study in patients with prodromal or mild Alzheimer’s disease. Presented at the 9th edition of Clinical Trials on Alzheimer’s Disease (CTAD). December 8–10, 2016, San Diego, CA, USA.

ANCOVA, analysis of covariance; ARIA-E, amyloid-related imaging abnormalities - vasogenic edema; CDR-SB, Clinical Dementia Rating—Sum of Boxes; MMSE, Mini-Mental State Examination; SE, standard error; SUVR, standard uptake value ratio. Nominal p values: *P<0.05; **P<0.01; ***P<0.001 vs placebo. Analyses based on observed data. ANCOVA for change from baseline with factors of treatment, laboratory APoE e4 status (carrier and non-carrier), and baseline CDR-SB. Efficacy analysis population is defined as all randomized subjects who received at least 1 dose of study medication and had at least 1 post-baseline questionnaire assessment. PD analysis population is defined as all randomized subjects who received at least 1 dose of study medication and had at least 1 post-baseline assessment of the parameter. Vigiletta et al. Aducanumab titration dosing regimen. 12-month interim analysis from PRIME, a randomized, double-blind, placebo-controlled Phase 1b study in patients with prodromal or mild Alzheimer’s disease. Presented at the 9th edition of Clinical Trials on Alzheimer’s Disease (CTAD). December 8–10, 2016, San Diego, CA, USA.
Safety
ARIA (amyloid related imaging abnormalities)

- The term ARIA refers to a spectrum of MRI signal abnormalities observed in the clinical trials of amyloid lowering agents.
- Image presentation as vasogenic edema (ARIA-E) or deposition of heme products (ARIA-H)
- Spontaneous ARIA-like events can occur in untreated AD and CAA
- The mechanism leading to ARIA are not fully elucidated
  - Putative pathophysiological basis thought to be increased vascular permeability triggered by removal of parenchymal/vascular amyloid
ARIA characteristics in PRIME

- Since the start of the PRIME study, ARIA-E has been observed in 46 of the 185 patients doses with aducanumab, with a cumulative incidence of 25% over the course of the study.
- Of the 46 patients with ARIA-E (± ARIA-H), 28 (61%) were asymptomatic and 18 (39%) had associated symptoms, which were typically mild.
- ARIA-E resolved on MRI in 44 of 46 patients and was ongoing in 2 patients at the time of withdrawal. In most cases resolving as assessed by MRI 4-12 weeks after onset.
- 8 patients experienced more than one event of ARIA-E (recurrent ARIA-E) which was similar to initial events.
- The incidence of ARIA-E in fixed dose cohorts was dose-dependent and occurred more frequently in ApoE ε4 carriers.
- The incidence of ARIA-E during the placebo-controlled period was lower in ApoE ε4 carriers receiving aducanumab titrated to 10mg/kg (35%) than in ApoE e4 carriers receiving fixed doses of 6mg/kg (43%) or 10mg/kg (55%) of aducanumab.
- The incidence of ARIA-H not accompanied by ARIA-E in the placebo-controlled period was low and similar across dose groups.
ARIA-E tends to occur early in the course of treatment with aducanumab
What we will learn (Phase 3)
# Aducanumab Phase 3 studies ENGAGE & EMERGE

<table>
<thead>
<tr>
<th>Studies</th>
<th>Two 18-month, randomized, double-blind, placebo-controlled, Phase 3 studies</th>
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</thead>
<tbody>
<tr>
<td>Geography</td>
<td>~360 sites in 20 countries</td>
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</tbody>
</table>
| Population | - MCI due to AD + mild AD dementia  
  - MMSE 24-30, CDR-G 0.5, RBANS ≤ 85, enriched using Amyloid PET |
| Doses | - Two dose levels (low & high) and placebo, randomized 1:1:1 |
| Duration | - 18 months; followed by long-term extension |
| Primary endpoint | - CDR sum of boxes |
| Other endpoints | - Secondary: MMSE, ADAS-Cog 13, ADCS-ADL-MCI  
  - Biomarkers: Aβ PET, tf-MRI, ASL-MRI, PBMC, blood-based biomarkers  
  - Sub-studies: Amyloid PET, Tau PET, CSF disease-related markers |
| Sample size | ~1605 per study |

**Strong engagement and high interest of clinical sites/community in aducanumab**
- ~12,500 patients screened
- Enrollment has completed July 2018

ADAS-Cog 13, Alzheimer’s Disease Assessment Scale-Cognitive Subscale (13-item); ADCS-ADL-MCI, Alzheimer’s Disease Cooperative Study-Activities of Daily Living Inventory (Mild Cognitive Impairment version); ASL-MRI, arterial spin labelling MRI; fMRI, functional MRI; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; PBMC, peripheral blood mononuclear cells; PET, positron-emission tomography; RBANS, Repeatable Battery for Assessment of Neuropsychological Status.

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