Aducanumab for the Treatment of Alzheimer’s Disease

US Food & Drug Administration
Peripheral and Central Nervous System Drugs Advisory Committee
November 6, 2020
Introduction

Alfred Sandrock, MD, PhD
Executive Vice President, Research and Development
Biogen
Introduction to Biogen

Motivated by need for new CNS treatments

Encouraged by advances in the science

Need is especially great in Alzheimer’s disease
β-Amyloid is a Key Pathological Hallmark of Alzheimer’s Disease

**β-Amyloid Aggregation Pathway**

- Monomer
- Oligomer
- Protofibril
- Fibril

Formation of oligomers on the fibril surface (“Secondary Nucleation”)

- Aducanumab

- Human genetic and clinico-pathologic evidence implicates β-amyloid in the pathogenesis of Alzheimer’s disease
- Downstream tau pathology leads to neurofibrillary tangles
- Lessons from prior programs targeting β-amyloid
  - Molecular binding characteristics are important
  - Aducanumab targets aggregated β-amyloid
Aducanumab Targets and Removes β-Amyloid From the Brain

- Aducanumab binds to aggregated forms of β-amyloid and β-amyloid plaques in brain tissue
- Preclinical studies showed that aducanumab entered the brain and was bound to brain parenchymal β-amyloid
- Substantial and dose-dependent removal of β-amyloid pathology
Aducanumab US Regulatory History

- IND opened for AD
- Special protocol assessment for phase 3 studies
- Fast track granted
- 4 formal FDA engagements
- BLA submission
- Futility announced

- Patients with biomarker-confirmed Alzheimer’s disease
- 10 mg/kg dosing robustly removed β-amyloid
Proposed Patient Population and Dosing Recommendation

**Proposed Indication**
Aducanumab is an amyloid beta targeting antibody indicated to delay clinical decline in patients with Alzheimer’s disease.

**Dosing and Administration**
10 mg/kg administered as an intravenous infusion over approximately one hour every four weeks following titration.
# Agenda

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<td>Executive Vice President, Research and Development</td>
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<td>Biogen</td>
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<td>Douglas Galasko, MD</td>
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<td>Samantha Budd Haeberlein, PhD</td>
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<td>Senior Vice President, Head of Neurodegeneration Development Unit</td>
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<td><strong>Safety</strong></td>
<td>Karen Smirnakis, MD, PhD, MPH</td>
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<td>Vice President, Head of Global Medical Safety</td>
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<td><strong>Clinical Perspective</strong></td>
<td>Anton P. Porsteinsson, MD</td>
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<td>University of Rochester Medical Center</td>
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Disease Background & Unmet Need

Douglas Galasko, MD
UC San Diego
Alzheimer’s Disease Presents a Significant Unmet Medical Need

- 5.8 million Americans suffer from Alzheimer’s disease
- Progressive neurological disorder resulting in memory loss, behavioral symptoms, and loss of ability to perform daily activities
- In advanced stages of dementia patients become completely dependent
- Alzheimer’s disease is ultimately fatal
- No available treatment that alters the course of disease
## Symptoms Along the Course of Alzheimer's Disease

<table>
<thead>
<tr>
<th>Stage (MMSE)</th>
<th>Cognition</th>
<th>Function</th>
<th>Behavior</th>
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<tbody>
<tr>
<td>Early (21-30)</td>
<td>Recall/learning, Word finding, Problem solving, Judgment, Calculation</td>
<td>Forgets details of conversation, Complex hobbies, Work, Driving, Money/shopping, Medications</td>
<td>Apathy, Withdrawal, Depressed mood, Anxiety, Irritability</td>
</tr>
<tr>
<td>Mid (10-20)</td>
<td>Recent memory, Language (names, paraphasias), Comprehension, Orientation, Visuospatial ability</td>
<td>Complete loss of Instrumental Activities of Daily Living, Gets lost, Misplaces things, Cannot be left alone</td>
<td>Delusions, Hallucinations, Agitation, Wandering, Insomnia</td>
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<tr>
<td>Late (&lt;10)</td>
<td>Very limited language, Attention, Apraxia</td>
<td>Loss of basic Activities of Daily Living, Eating with utensils, Loss of social graces</td>
<td>Agitation (verbal or physical), Outbursts, Insomnia</td>
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Adapted from Galasko D. Eur J Neurol. 1998;5(suppl 4):S9-S17. John Wiley and Sons. Copyright 1998 Lippincott Williams & Wilkins. All rights reserved.
Alzheimer’s Pathology Progresses and Precedes Symptoms

Time/Disease Progression

- Abnormal
  - β-amyloid
  - τ-mediated neuronal injury and dysfunction
  - Structural brain changes
  - Clinical impairment

Biomarker and Clinical Presentation

Cognitively normal - MCI - Dementia

Phase 3 population

The Two Pathological Hallmarks of Alzheimer’s Disease in the Brain Are Aβ Plaques and Neurofibrillary Tangles

1) Amyloid beta peptides are released extraneuronally as monomers
2) Aggregation of Aβ
3) Intraneuronal tau phosphorylation and aggregation
4) Synaptic dysfunction, inflammation and neuronal death

Aβ=amyloid beta; APP=amyloid precursor protein.
Aging and Genetic Factors Underlie Alzheimer’s Disease

• Increasing age has the largest impact on risk

• ApoE4 gene is the strongest known genetic risk factor for late-onset Alzheimer’s disease

• Autosomal dominant mutations with young age at onset account for 1% of Alzheimer’s disease cases

• In both familial and sporadic Alzheimer’s disease, changes in amyloid production and/or clearance are important factors
Learnings From Prior Therapeutic Programs Targeting Amyloid

• There have been many therapeutic approaches to targeting the amyloid pathways, including production clearance and aggregation

• **Major Learnings:**
  - **Target:** By targeting aggregated forms of Aβ with specificity and high affinity, Aducanumab provides an opportunity to disrupt the pathological cascade that leads to the clinical symptoms of Alzheimer’s disease
  - **Timing:** Therapeutic approaches to target amyloid may be more successful if initiated earlier in disease, prior to extensive neurodegeneration
Current Medications for Alzheimer’s Disease

• Approved therapies for Alzheimer’s disease are
  – Cholinesterase inhibitors (donepezil, galantamine, rivastigmine)
  – NMDA antagonists (memantine)
• Approved therapies have a modest effect on cognitive symptoms
• No therapies are approved for earlier stages of disease (ie, MCI due to Alzheimer’s disease)
• These symptomatic treatments do not impact brain pathology
Why Do We Need a Drug Like Aducanumab for Alzheimer’s Disease?

• Disabling and ultimately fatal dementing disease
• Increasing incidence due to an aging population
• Enormous economic and societal burden
• Delaying the onset and progression of Alzheimer’s disease by 2 years may result in a 22.5% reduction in the global burden by the year 2050
• Aducanumab has the potential to slow clinical decline, extending the time people can live with conserved cognitive abilities, preserving autonomy in activities of daily living, and lessening behavioral symptoms

Clinical Development

Samantha Budd Haeberlein, PhD
Senior Vice President, Head Neurodegeneration Development Unit
Biogen
## Studies Supporting the Substantial Efficacy of Aducanumab

<table>
<thead>
<tr>
<th>Study</th>
<th>Description</th>
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<tbody>
<tr>
<td>Study 302</td>
<td>A positive study with robust and internally consistent results</td>
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<td>Study 301</td>
<td>A failed study with reasons for differences between studies understood</td>
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<td>Consistent dosing at 10 mg/kg yielded positive treatment effect</td>
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<tr>
<td>Study 103</td>
<td>An independent study providing consistent evidence</td>
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Aducanumab: Targeting Alzheimer’s Disease Pathology

Aducanumab Treatment: Reduced Progression of Alzheimer’s Disease

No treatment
Aducanumab Is Differentiated From the First Generation of Anti-\(\alpha\beta\) Antibodies

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<tr>
<th>Molecular Characteristics of Aducanumab</th>
<th>Key Clinical Trial Design Elements</th>
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<tr>
<td>• Specificity for neurotoxic aggregated forms of (\alpha\beta)</td>
<td>• Inclusion of patients with biomarker-confirmed early symptomatic Alzheimer’s disease</td>
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<tr>
<td>• Effector-function enabling immune cell-mediated clearance of aggregated (\alpha\beta)</td>
<td>• Demonstration of robust reduction in pathology</td>
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<td></td>
<td>• Appropriate clinical outcome measures</td>
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</table>

• Aducanumab was the first of this generation of antibodies to demonstrate proof of concept before initiating phase 3 trials
• Aducanumab is the only program at this time to have read out with positive results in phase 3 trials
Molecular Characteristics of Aducanumab Contribute to Its Binding Selectivity and Affects the Aggregation Pathway

Shallow and compact epitope of Aducanumab contributes to its selectivity for Aβ aggregates [Arndt 2018]

Binding of Aducanumab to fibrils interferes with aggregation process and reduces formation of neurotoxic Aβ oligomers [Linse 2020]

Beta-Amyloid Aggregation Pathway

Monomer → Oligomer → Protofibril + Oligomer → Fibril

Formation of oligomers on the fibril surface ("Secondary Nucleation")

Aducanumab Is a Human IgG$_1$ Monoclonal Antibody Highly Selective for Aβ Aggregates

**Diagram:**
- Binding to insoluble fibrillar and soluble oligomeric Aβ1-42

**Graph:**
- **Hippocampus**
  - Soluble Aβ (6E10)
  - Insoluble Aβ (ThioS)
- Dose, mg/kg: PBS, 0.3, 1, 3, 10, 30
- *p<0.05, compared with control

Aducanumab Clinical Development Program

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**Phase 1**

- Study 101, n=53: Single ascending dose
- Study 102: Bioavailability, n=28
- Study 104, n=21: Japanese phase 1

**Phase 1b/2**

- Study 103, n=197: Proof-of-Concept
- Study 103 Long-term extension (LTE)

**Phase 3/3b**

- Study 301, n=1653: Study 301 Long-term extension (LTE)
- Study 302, n=1643: Study 302 Long-term extension (LTE)
- Study 304, n=Max 2400

- Study 205: Safety study, n=52
Study 103
Study 103 Design

- Randomized, multicenter, 12-month, double-blind, placebo-controlled study to assess safety, tolerability, and pharmacokinetic and pharmacodynamic effects of aducanumab in patients with Alzheimer’s disease

Endpoints
- Primary endpoint: safety and tolerability
- Secondary endpoints: serum PK, immunogenicity, change in amyloid PET (Week 26)
- Exploratory endpoints included CDR–SB, MMSE, change in amyloid PET (Week 54)

Treatment arms
- Placebo\(^a\) (n=48)
- 1 mg/kg (n=31)
- 3 mg/kg (n=32)
- 6 mg/kg (n=30)
- 10 mg/kg (n=32)

Titration ApoE $\varepsilon$4 carriers; 1→10 mg/kg (n=23)

Population
- Prodromal Alzheimer’s disease & mild Alzheimer’s disease dementia
- MMSE ≥20-30
- Positive amyloid PET

Randomization: 3:1 active:placebo; fixed-dose within cohorts stratified by ApoE $\varepsilon$4 status with 14 total doses in each arm

\(^a\) Pooled placebo group.
Aducanumab Target Engagement: Dose- and Time-Dependent Reduction in Amyloid Plaque as Measured by PET

Study 103

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

- Baseline
- One year
- Placebo
- 3 mg/kg
- 6 mg/kg
- 10 mg/kg

Composite SUVR adjusted mean change from baseline (±S.E.)

- Diff. from placebo
  - Week 54
  - -0.064 *
  - -0.145 ***
  - -0.185 ***
  - -0.220 ***
  - -0.277 ***

Analysis visit, week

- 0
- 26
- 54

<table>
<thead>
<tr>
<th>Aducanumab</th>
<th>Placebo</th>
<th>1 mg/kg</th>
<th>3 mg/kg</th>
<th>6 mg/kg</th>
<th>10 mg/kg</th>
<th>Titration</th>
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<tr>
<td></td>
<td>42</td>
<td>42</td>
<td>26</td>
<td>29</td>
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* p<0.05, **p<0.01, ***p<0.001 (nominal).

**Clinical Proof of Concept: Effect of Aducanumab on Clinical Decline as Measured by CDR-SB and MMSE**

**Study 103**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Placebo</th>
<th>1 mg/kg</th>
<th>3 mg/kg</th>
<th>6 mg/kg</th>
<th>Titration</th>
<th>10 mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Change in CDR-SB</strong></td>
<td></td>
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</tr>
<tr>
<td>Adjusted mean change from baseline at Week 54 (SE)</td>
<td>0.0</td>
<td>-2.5</td>
<td>-3.0</td>
<td>-3.5</td>
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</tbody>
</table>

* p<0.05 (nominal)

<table>
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<tr>
<th>Condition</th>
<th>Placebo</th>
<th>1 mg/kg</th>
<th>3 mg/kg</th>
<th>6 mg/kg</th>
<th>Titration</th>
<th>10 mg/kg</th>
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</thead>
<tbody>
<tr>
<td><strong>Change in MMSE</strong></td>
<td></td>
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<tr>
<td>Adjusted mean change from baseline at Week 52 (SE)</td>
<td>0.0</td>
<td>-2.5</td>
<td>-3.0</td>
<td>-3.5</td>
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</tbody>
</table>

* p<0.05 (nominal)
Strong Correlation Between Aβ Reduction and Reduction in Clinical Decline
Study 103

![Graph showing the correlation between Aβ reduction and clinical decline.](image-url)
## Design Elements From Study 103 Were Implemented to Improve the Probability of Success in Phase 3

<table>
<thead>
<tr>
<th>Patient population</th>
<th>Early symptomatic Alzheimer’s disease (MMSE, 20-30 → 24-30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical endpoints</td>
<td>CDR-SB was confirmed to be sensitive in early Alzheimer’s disease</td>
</tr>
<tr>
<td>Diagnostic accuracy</td>
<td>Supported by detection of amyloid pathology</td>
</tr>
<tr>
<td>Dose</td>
<td>10 mg/kg was identified as the most efficacious dose by target engagement and clinical results</td>
</tr>
<tr>
<td>Dosing regimen</td>
<td>ARIA, an AE, was confirmed to be dose-dependent. Titration was identified as a mitigation strategy</td>
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</tbody>
</table>
Efficacy of Aducanumab

Samantha Budd Haeberlein, PhD
Senior Vice President, Head Neurodegeneration Development Unit
Biogen
## Aducanumab Phase 3 Trial Design

### Studies 301 and 302

<table>
<thead>
<tr>
<th>Studies</th>
<th>Two 18-month, randomized, double-blind, placebo-controlled, Phase 3 studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Geography/Sample size</td>
<td>3285 patients at 348 sites in 20 countries</td>
</tr>
<tr>
<td>Population</td>
<td>• Early Alzheimer’s disease (MCI due to Alzheimer’s disease + mild Alzheimer’s disease dementia)</td>
</tr>
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<td></td>
<td>- MMSE 24-30, CDR-G 0.5, RBANS ≤ 85, with confirmed amyloid pathology</td>
</tr>
<tr>
<td>Doses</td>
<td>• Two dosing regimens (low and high) and placebo; randomized 1:1:1</td>
</tr>
<tr>
<td>Primary endpoint</td>
<td>• CDR-SB at 18 months</td>
</tr>
<tr>
<td>Other endpoints</td>
<td>• Secondary: MMSE, ADAS-Cog 13, ADCS-ADL-MCI</td>
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<td></td>
<td>• Sub-studies: amyloid PET, tau PET, CSF disease-related biomarkers</td>
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Countries with active sites included:
Australia, Austria, Belgium, Canada, Denmark, Finland, France, Germany, Italy, Japan, the Netherlands, Poland, Portugal, South Korea, Spain, Sweden, Switzerland, Taiwan, United Kingdom, United States
Clinical Endpoints Measure Distinct, Important Symptoms of Cognition, Function, and Behavior

Five clinical rating scales were used in Studies 301 and 302:

- Validated and widely used in early Alzheimer’s disease
- Covers the full scope of symptoms experienced by patients with Alzheimer’s disease
- Include a range of paradigms:
  - Expert clinical judgements based on patient examination and caregiver input
  - Patient and caregiver reports
  - Cognitive performance tests
- Together they cover a range of important and distinct dimensions with minimal overlap

Overlap of scales is only 5% to 25%

- ADAS-Cog 13
- MMSE
- ADCS-ADL-MCI
- CDR
- NPI
## Baseline Demographics and Disease Characteristics
### Studies 301 and 302

<table>
<thead>
<tr>
<th></th>
<th>Study 301</th>
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<th>Study 302</th>
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</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo N=545</td>
<td>Low dose N=547</td>
<td>High dose N=545</td>
<td>Total N=1647</td>
<td>Placebo N=548</td>
<td>Low dose N=543</td>
<td>High dose N=547</td>
<td>Total N=1638</td>
</tr>
<tr>
<td>Age, years, mean (SD)</td>
<td>69.8 (7.72) 70.4 (6.96) 70.0 (7.65) 70.1 (7.45)</td>
<td>70.8 (7.40) 70.6 (7.45) 70.6 (7.47) 70.7 (7.43)</td>
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<tr>
<td>Sex, female, n (%)</td>
<td>287 (52.7) 284 (51.9) 292 (52.6) 863 (52.4)</td>
<td>290 (52.9) 269 (49.5) 284 (51.9) 843 (51.5)</td>
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<td>Race, n (%)</td>
<td>Asian 55 (10.1) 55 (10.1) 65 (11.7) 175 (10.6)</td>
<td>47 (8.6) 39 (7.2) 42 (7.7) 128 (7.8)</td>
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<td>White 413 (75.8) 412 (75.3) 413 (74.4) 1238 (75.2)</td>
<td>431 (78.6) 432 (79.6) 422 (77.1) 1285 (78.4)</td>
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<tr>
<td>Education, years, mean (SD)</td>
<td>14.7 (3.66) 14.6 (3.77) 14.6 (3.72) 14.6 (3.71)</td>
<td>14.5 (3.68) 14.5 (3.63) 14.5 (3.60) 14.5 (3.63)</td>
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<tr>
<td>AD medications used, n (%)</td>
<td>299 (54.9) 317 (58.0) 313 (56.4) 929 (56.4)</td>
<td>282 (51.5) 281 (51.7) 285 (52.1) 848 (51.8)</td>
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<tr>
<td>ApoE ε4, n (%)</td>
<td>Carriers 376 (69.0) 391 (71.5) 378 (68.1) 1145 (69.5)</td>
<td>368 (67.2) 362 (66.7) 365 (66.7) 1095 (66.8)</td>
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<td>Non-carriers 167 (30.6) 156 (28.5) 176 (31.7) 499 (30.3)</td>
<td>178 (32.5) 178 (32.8) 181 (33.1) 537 (32.8)</td>
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<tr>
<td>Clinical stage, n (%)</td>
<td>MCI due to AD 443 (81.3) 440 (80.4) 442 (79.6) 1325 (80.4)</td>
<td>446 (81.4) 452 (83.2) 438 (80.1) 1336 (81.6)</td>
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<td>Mild AD 102 (18.7) 107 (19.6) 113 (20.4) 322 (19.6)</td>
<td>102 (18.6) 91 (16.8) 109 (19.9) 302 (18.4)</td>
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<tr>
<td>CDR-SB, mean (SD)</td>
<td>2.40 (1.012) 2.43 (1.014) 2.40 (1.010) 2.41 (1.012)</td>
<td>2.47 (0.999) 2.46 (1.011) 2.51 (1.053) 2.48 (1.021)</td>
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<tr>
<td>MMSE, mean (SD)</td>
<td>26.4 (1.73) 26.4 (1.78) 26.4 (1.77) 26.4 (1.76)</td>
<td>26.4 (1.78) 26.3 (1.72) 26.3 (1.68) 26.3 (1.73)</td>
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Phase 3 Target Dose: 10 mg/kg With 6-Month Titration
Studies 301 and 302

24-week titration to reduce incidence of ARIA
14 doses of 10 mg/kg as in Study 103
Early enrolled patients in the high-dose arm received a lower dose

<table>
<thead>
<tr>
<th>ApoE ε4+ Low dose</th>
<th>3 mg/kg</th>
<th>1 mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>ApoE ε4- Low dose</td>
<td>6 mg/kg</td>
<td>3 mg/kg</td>
</tr>
<tr>
<td>ApoE ε4+ and ApoE ε4- High dose</td>
<td>10 mg/kg</td>
<td>6 mg/kg</td>
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</table>

Median cumulative dose at Week 78:
- 56 mg/kg
- 98 mg/kg
- 153 mg/kg (post-PV4)
- 116 mg/kg (pre-PV4)

Expected # of 10 mg/kg in high-dose group:
- by Week 26: 1 dose
- by Week 50: 7 doses
- by Week 78: 14 doses

Phase 3 Enrollment and Timing of Protocol Amendment Affecting Dosing
Studies 301 and 302

Consent to Protocol Version 4 18-month period

Futility Analysis

Overlap with post-PV4 group was minimal
March 2019: Prespecified Futility Analysis Led to Early Termination

- Two key assumptions did not hold, and futility analysis did not accurately predict the future results
- Assumption 1: Identically designed studies would lead to similar study results. Therefore, pooled conditional power is appropriate

<table>
<thead>
<tr>
<th>Futility Assessment</th>
<th>301</th>
<th>302</th>
</tr>
</thead>
<tbody>
<tr>
<td>CDR-SB, diff from placebo (%)</td>
<td>0.22 (15%)</td>
<td>-0.28 (-18%)</td>
</tr>
<tr>
<td>Conditional power (pooled)</td>
<td>0</td>
<td>12%</td>
</tr>
<tr>
<td>Futility criteria (pooled)</td>
<td>Met</td>
<td>Met</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Post-Hoc Assessment</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Conditional power (unpooled)</td>
<td>0</td>
<td>59%</td>
</tr>
<tr>
<td>Futility criteria (unpooled)</td>
<td>Met</td>
<td>Not Met</td>
</tr>
</tbody>
</table>
March 2019: Prespecified Futility Analysis Led to Early Termination

- Two key assumptions did not hold, and futility analysis did not accurately predict the future results
- Assumption 2: Treatment effect will remain consistent over time

<table>
<thead>
<tr>
<th>Futility Analysis</th>
<th>301</th>
<th>302</th>
</tr>
</thead>
<tbody>
<tr>
<td>CDR-SB diff from placebo</td>
<td>0.22 (15%)</td>
<td>-0.28 (-18%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Final Analysis</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>CDR-SB diff from placebo</td>
<td>0.03 (2%)</td>
<td>-0.39 (-22%)</td>
</tr>
</tbody>
</table>

- Improved treatment effect over time in both studies
Percent of Patients that had Opportunity to Complete Planned Clinical Assessments at Termination

Studies 301 and 302

- Study 301
- Study 302
Study 302
Curve shows adjusted mean for placebo treated group, ITT population: placebo-controlled period excluding data after 20Mar2019 (221AD302). Shaded area is 95% CI.
High Dose Met Primary Objective of CDR-SB at Week 78
Study 302

<table>
<thead>
<tr>
<th>% Difference from placebo (95% CI)</th>
<th>( p ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low-dose aducanumab</td>
<td>-15%</td>
</tr>
<tr>
<td>(-0.26, 0.041)</td>
<td>( p=0.0901 )</td>
</tr>
<tr>
<td>High-dose aducanumab</td>
<td>-22%</td>
</tr>
<tr>
<td>(-0.39, -0.086)</td>
<td>( p=0.0120 )</td>
</tr>
</tbody>
</table>

\( n = \) numbers of randomized and dosed participants included in the analysis
Data Were Consistent Across Prespecified Primary and Supplementary Datasets

Study 302

CDR-SB

% Difference vs placebo

Low-dose aducanumab
High-dose aducanumab

Difference from placebo (95% CI)
p value

Low-dose
n=543
High-dose
n=547
Low-dose
n=329
High-dose
n=340
Low-dose
n=543
High-dose
n=547

-15% (-0.569, 0.041) p=0.0901
-22%
(-0.694, -0.086) p=0.0120
-17% (-0.614, 0.070) p=0.1188
-22% (-0.702, -0.022) p=0.0368
-12% (-0.510, 0.064) p=0.1273
-25%
(-0.723, -0.149) p=0.0029

n=numbers of randomized and dosed participants included in the analysis
Missing Data Did Not Compromise the Validity of Results
Study 302

CDR-SB

Primary Analysis  Censoring after intercurrent events  Copy increment from reference  Jump to reference

<table>
<thead>
<tr>
<th></th>
<th>Low-dose</th>
<th>High-dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Difference vs placebo</td>
<td>n=543</td>
<td>n=547</td>
</tr>
<tr>
<td>Low-dose</td>
<td>-15%</td>
<td>-15%</td>
</tr>
<tr>
<td>High-dose</td>
<td>-0.26 (-0.569, 0.041)</td>
<td>-0.24 (-0.554, 0.079)</td>
</tr>
<tr>
<td></td>
<td>p=0.0901</td>
<td>p=0.1415</td>
</tr>
<tr>
<td>Low-dose</td>
<td>-22%</td>
<td>-25%</td>
</tr>
<tr>
<td>High-dose</td>
<td>-0.39 (-0.694, -0.086)</td>
<td>-0.41 (-0.724, -0.090)</td>
</tr>
<tr>
<td></td>
<td>p=0.0120</td>
<td>p=0.0119</td>
</tr>
</tbody>
</table>

n = numbers of randomized and dosed participants included in the analysis

% Difference from placebo (95% CI)  p value

% Low-dose aducanumab  % High-dose aducanumab
All Items Measured in Primary Endpoint (CDR-SB) Were Improved by High-Dose Aducanumab

Study 302

Adjusted mean change from baseline at week 78

- Orientation: 0.26 (Placebo), 0.34 (High-dose aducanumab), Treatment difference: -0.08 (-24%)
- Community affairs: 0.24 (Placebo), 0.31 (High-dose aducanumab), Treatment difference: -0.07 (-23%)
- Home and hobbies: 0.23 (Placebo), 0.29 (High-dose aducanumab), Treatment difference: -0.07 (-24%)
- Judgment and problem solving: 0.21 (Placebo), 0.28 (High-dose aducanumab), Treatment difference: -0.07 (-25%)
- Memory: 0.17 (Placebo), 0.25 (High-dose aducanumab), Treatment difference: -0.07 (-28%)
- Personal care: 0.17 (Placebo), 0.2 (High-dose aducanumab), Treatment difference: -0.03 (-15%)
High-dose Aducanumab Met All Clinical Endpoints Assessing Cognition and Function at Week 78

Study 302

Primary Endpoint

<table>
<thead>
<tr>
<th>CDR-SB</th>
<th>MMSE</th>
<th>ADAS-Cog13</th>
<th>ADCS-ADL-MCI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low-dose</td>
<td>High-dose</td>
<td>Low-dose</td>
<td>High-dose</td>
</tr>
<tr>
<td>-15% (-0.569, 0.041)</td>
<td>-22% (-0.694, -0.086)</td>
<td>-18% (0.00, 1.13)</td>
<td>-14% (-1.76, 0.36)</td>
</tr>
<tr>
<td>p=0.0901</td>
<td>p=0.0120</td>
<td>p=0.0493</td>
<td>p=0.1962</td>
</tr>
</tbody>
</table>

Secondary Endpoints

- MMSE: 3%
- ADAS-Cog13: -0.1 (-0.65, 0.48) p=0.7578
- ADCS-ADL-MCI: -0.7 (0.00, 1.13) p=0.1962

n=numbers of randomized and dosed participants included in the analysis
Aducanumab Reduced Functional Decline in Activities of Daily Living: ADCS-ADL-MCI

Study 302

- Use a telephone: -0.53
- Talk about current events: -0.39
- Use household appliance: -0.38
- Travel: -0.34
- Balance banking: -0.33
- Watch television: -0.28
- Go shopping: -0.27
- Read more than 5 minutes: -0.26
- Find personal belongings: -0.22
- Make a meal: -0.22
- Select first clothes: -0.21
- Clean room: -0.2
- Perform pastime: -0.2
- Keep appointments: -0.19
- Write things down: -0.17
- Clean laundry: -0.14
- Left on his/her own: -0.14
- Usual dressing: -0.1

Treatment difference (%):
- Placebo:
  - 0.14 (-26%)
  - 0.15 (-39%)
  - 0.22 (-65%)
  - 0.11 (-33%)
  - 0.07 (-23%)
  - 0.14 (-50%)
  - 0.09 (-33%)
  - 0.17 (-65%)
  - 0.12 (-55%)
  - 0.20 (-91%)
  - 0.13 (-62%)
  - 0.14 (-70%)
  - 0.08 (-40%)
  - 0.02 (-11%)
  - 0.04 (-29%)
  - 0.04 (-29%)
  - 0.05 (-42%)
  - 0.04 (-44%)

High-dose aducanumab:

Adjusted mean change from baseline at week 78:

- Placebo: [-0.53, -0.39, -0.38, -0.34, -0.33, -0.28, -0.27, -0.26, -0.22, -0.22, -0.21, -0.2, -0.2, -0.19, -0.17, -0.14, -0.14, -0.1, -0.12, -0.12, -0.07, -0.09, -0.06]
- High-dose aducanumab: [-0.53, -0.39, -0.38, -0.34, -0.33, -0.28, -0.27, -0.26, -0.22, -0.22, -0.21, -0.2, -0.2, -0.19, -0.17, -0.14, -0.14, -0.1, -0.12, -0.12, -0.07, -0.09, -0.06]
Treatment Effect Observed in Exploratory Clinical Endpoint of NPI-10 Assessing Behavior at Week 78
Study 302

Caregivers of patients who received high-dose aducanumab reported 84% less burden compared with caregivers of patients who received placebo.

Neuropsychiatric Inventory 10 (NPI-10)

-33%  
-0.5 (-1.62, 0.64)  
p=0.3921

Low-dose  
n=543

High-dose  
n=547

Difference from placebo (95% CI)  
p value

-87%  
-1.3 (-2.45, -0.20)  
p=0.0215

n=numbers of randomized and dosed participants included in the analysis
Study 302 Amyloid PET Confirms Dose-Dependent Target Engagement as Demonstrated in Study 103

Study 302

![Graph showing adjusted mean change from baseline over analysis visits for Placebo, Low-dose aducanumab, and High-dose aducanumab.](image)

- Placebo: 159 (Week 0), 129 (Week 26), 93 (Week 78)
- Low-dose aducanumab: 159 (Week 0), 129 (Week 26), 100 (Week 78)
- High-dose aducanumab: 170 (Week 0), 138 (Week 26), 109 (Week 78)

*** p<0.001 (nominal).
Aducanumab Reduced Biomarkers of Alzheimer’s Disease-Specific Tau Pathophysiology

Study 302

CSF p-Tau

Adjusted mean change from Baseline, pg/ml (SE)

Placebo n=28
Low-dose n=33
High-dose n=17

Change from baseline at Week 78, pg/ml

Cumulative dose by Week 78, mg/kg

Treatment: ● Placebo  ○ Low-dose  ▲ High-dose

** p<0.01, *** p<0.001 (nominal).
n=numbers of randomized and dosed participants included in the analysis
Aducanumab Reduced Biomarkers of Neurodegeneration

Study 302

CSF t-Tau

Adjusted mean change from Baseline, pg/ml (SE)

Placebo n=28
Low-dose n=33
High-dose n=17

* p<0.05, ** p<0.01 (Nominal)

n=numbers of randomized and dosed participants included in the analysis
Aducanumab Reduced Biomarkers of Tau Neurofibrillary tangles in the Brain
Pooled Data, Studies 301 and 302

* p<0.05, *** p<0.001 (nominal).

n=numbers of randomized and dosed participants included in the analysis
Higher Cumulative Dose of Aducanumab was Correlated with a Greater Reduction of Tau Neurofibrillary Tangles

Pooled Data, Studies 301 and 302

Adjusted mean change from baseline (SE) * p<0.05, *** p<0.001 (nominal).

n=numbers of randomized and dosed participants included in the analysis
Aducanumab-related Biomarker Changes Are Associated With Slowing in Clinical Decline

Study 302

**Aducanumab**

- **β-amyloid (Composite SUVR)**
  - 0.19 * (CDR-SB)
  - 0.20 * (ADAS-Cog13)
- **Tau (CSF p-Tau)**
  - 0.52 *
  - 0.11 (ADAS-Cog13)
- **Clinical outcomes**
  - -0.24 * (MMSE)
  - -0.29 * (ADCS-ADL-MCI)
  - -0.39 * (MMSE)
  - -0.44 * (ADCS-ADL-MCI)

*p < 0.05 (nominal)

All associations are partial Spearman correlation of change from baseline to Week 78 between each variable.
Internal Consistency of Clinical Endpoints and Aβ Reduction in Prespecified Subgroups

Study 302 Subgroup Results

- Subgroup factors: region, age, sex, ApoE ε4 carrier status, baseline clinical stage, baseline MMSE, and baseline AD symptomatic con-med use

- Numeric advantage of high dose vs placebo on 79 of 80 comparisons (5 clinical endpoints × 16 prespecified demographic and baseline disease characteristic subgroups)
  - For CDR-SB, numeric advantage of high dose vs placebo in 16 of 16 subgroups

- Significant advantage of high dose vs placebo on amyloid PET in all 13 prespecified subgroups
Precise Dose-Exposure-Response for β-Amyloid PET Study 302

**Exposure- SUVr Relationship**

- 1(2)-3-mg/kg (Q4W)
- 1(2)-3(2)-6-mg/kg (Q4W)
- 1(2)-3(2)-6(2)-10-mg/kg (Q4W)

**Impact of Dose Suspension on Amyloid PET SUVr**

- 1(2)-3(2)-6(2)-10-mg/kg (Q4W)
- ARIA-E (impact)

UI=Uncertainty interval.
Study 302, as in Study 103, showed that greater mean Aβ reduction led to slowing of clinical decline.

Studies 103 and 302
Summary of Study 302

• Study 302 met its primary and secondary objectives in the high-dose arm
• Treatment effects were internally consistent across subgroups, and validity was not compromised by departures from statistical assumptions
• An intermediate effect was observed in the low-dose group, indicative of a dose-response relationship
• Substantial effects on objective measures of underlying Alzheimer’s disease pathophysiology
Study 301
Study Did Not Meet Primary and Secondary Clinical Endpoints

Study 301

<table>
<thead>
<tr>
<th>Primary Endpoint</th>
<th>CDR-SB</th>
<th>2%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Difference vs placebo</td>
<td>-12%</td>
<td>-0.18</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(-0.469, 0.110)</td>
<td>p=0.2250</td>
</tr>
<tr>
<td>p=0.8330</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Secondary Endpoints</th>
<th>MMSE</th>
<th>ADAS-Cog-13</th>
<th>ADCS-ADL-MCI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Difference from placebo</td>
<td>-6%</td>
<td>-11%</td>
<td>-18%</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(-0.62, 0.49)</td>
<td>(-1.6067, 0.4309)</td>
<td>(-0.25, 1.61)</td>
</tr>
<tr>
<td>p value</td>
<td>0.8106</td>
<td>0.2578</td>
<td>0.1506</td>
</tr>
</tbody>
</table>

- Low-dose aducanumab
- High-dose aducanumab

n=numbers of randomized and dosed participants included in the analysis
Amyloid PET Demonstrated Dose-Dependent Target Engagement With High-Dose Group Lower Than in Study 302

Study 301

**Mean cumulative dose at Week 78**
- Study 301: 109.1 mg/kg
- Study 302: 118.3 mg/kg

**Adjusted mean change from baseline (±SE)**

- Placebo: -0.167
- Low-dose aducanumab: -0.232
- High-dose aducanumab: -0.278

**Analysis visit, week**
- 0: Placebo 204, Low-dose aducanumab 198, High-dose aducanumab 183
- 26: Placebo 168, Low-dose aducanumab 169, High-dose aducanumab 156
- 78: Placebo 124, Low-dose aducanumab 138, High-dose aducanumab 112

*** p<0.001 (nominal).

n=numbers of randomized and dosed participants included in the analysis
Aducanumab Reduced Tau Pathophysiology in Study 301 With High-Dose Group Lower Than in Study 302

Study 301

**Tau pathophysiology**

**CSF p-Tau**

- Adjusted mean change from baseline, pg/ml (SE)
  - Placebo: n=15
  - Low-dose: n=20
  - High-dose: n=18

**Change from baseline at Week 78, pg/mL**

- Cumulative dose by Week 78, mg/kg

- Treatment: • Placebo ℹ️ Low-dose ▲ High-dose

n=numbers of randomized and dosed participants included in the analysis
Aducanumab Reduced Tau Pathophysiology in Study 301 With High-Dose Group Lower Than in Study 302

Study 301

Neurodegeneration

Adjusted mean change from baseline, pg/ml (SE)

CSF t-Tau

<table>
<thead>
<tr>
<th>Treatment</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>14</td>
</tr>
<tr>
<td>Low-dose</td>
<td>18</td>
</tr>
<tr>
<td>High-dose</td>
<td>16</td>
</tr>
</tbody>
</table>

Change from baseline at Week 78, pg/ml

Cumulative dose by Week 78, mg/kg

Treatment:  
- Placebo
- Low-dose
- High-dose

n=numbers of randomized and dosed participants included in the analysis
Study 301 High-Dose Group Diverged From an Otherwise Consistent Association Between Aβ Reduction and Slowing of Clinical Decline

Studies 301, 302, and 103
Summary of Study 301

- Study 301 failed to meet its primary or secondary objectives
# Summary of Efficacy Results
## Studies 301, 302, and 103

<table>
<thead>
<tr>
<th></th>
<th>Study 301</th>
<th></th>
<th>Study 302</th>
<th></th>
<th>Study 103</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo decline</td>
<td>Low dose</td>
<td>High dose</td>
<td>Placebo decline</td>
<td>Low dose</td>
<td>High dose</td>
</tr>
<tr>
<td></td>
<td>N=545</td>
<td>N=547</td>
<td>N=545</td>
<td>N=548</td>
<td>N=543</td>
<td>N=547</td>
</tr>
<tr>
<td>CDR-SB</td>
<td>n=333</td>
<td>1.56</td>
<td>-0.18 (-12%)</td>
<td>0.2250</td>
<td>n=295</td>
<td>0.03 (2%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>n=311</td>
<td></td>
<td></td>
<td>n=290</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>-0.26 (-15%)</td>
<td>0.0901</td>
<td></td>
<td>-0.39 (-22%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>n=288</td>
<td></td>
<td></td>
<td>n=299</td>
</tr>
<tr>
<td>MMSE</td>
<td>n=332</td>
<td>-3.5</td>
<td>0.2 (-6%)</td>
<td>0.4795</td>
<td>n=297</td>
<td>-0.1 (3%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>n=334</td>
<td></td>
<td></td>
<td>n=293</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.1 (-3%)</td>
<td></td>
<td></td>
<td>0.6 (-18%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>n=288</td>
<td></td>
<td></td>
<td>n=299</td>
</tr>
<tr>
<td>ADAS-Cog13</td>
<td>n=331</td>
<td>5.140</td>
<td>-0.583 (-11%)</td>
<td>0.2536</td>
<td>n=294</td>
<td>-0.588 (-11%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>n=332</td>
<td></td>
<td></td>
<td>n=290</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>-0.701 (-14%)</td>
<td>0.1962</td>
<td></td>
<td>-1.400 (-27%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>n=287</td>
<td></td>
<td></td>
<td>n=293</td>
</tr>
<tr>
<td>ADCS-ADL-MCI</td>
<td>n=331</td>
<td>-3.8</td>
<td>0.7 (-18%)</td>
<td>0.1225</td>
<td>n=298</td>
<td>0.7 (-18%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>n=330</td>
<td></td>
<td></td>
<td>n=286</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.7 (-16%)</td>
<td></td>
<td></td>
<td>1.7 (-40%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>n=283</td>
<td></td>
<td></td>
<td>n=296</td>
</tr>
<tr>
<td>NPI-10</td>
<td>n=327</td>
<td>1.2</td>
<td>-1.0 (-83%)</td>
<td>0.0460</td>
<td>n=297</td>
<td>0.1 (8%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>n=326</td>
<td></td>
<td></td>
<td>n=283</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>-0.5 (-33%)</td>
<td></td>
<td></td>
<td>-1.3 (-87%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>n=282</td>
<td></td>
<td></td>
<td>n=291</td>
</tr>
</tbody>
</table>

N=numbers of randomized and dosed participants included in the analysis
n=numbers of randomized and dosed participants included in the analysis with endpoint assessment at Week 78
(Week 54/52 for 103)
Understanding Why Study 301 High-Dose Arm Was Discordant

Samantha Budd Haeberlein, PhD
Senior Vice President, Head Neurodegeneration Development Unit
Biogen
Results in the Two Trials Were Partially Discordant
Study 301 and 302

- Low-dose: clinical
- Low-dose: β-amyloid PET
- Low-dose: CSF Tau
- 302 High-dose
- Exposure response relationship

Supports efficacy of aducanumab

301 High-dose

301 high dose discordant with the set
Differences in Study 301 Are Sufficiently Understood so as Not to Detract From Study 302

• Demographics, disease characteristics, and frequency, severity and management of ARIA were all similar between studies.

• Differences between studies were largely driven by:
  – Lower exposure to 10 mg/kg dosing in Study 301
  – Imbalance in number and distribution of rapid progressing Alzheimer’s disease patients
10 mg/kg Is Important for Efficacy and Is Influenced by Multiple Factors

- Missed doses, study withdrawal
- ARIA management
- 14 doses of 10 mg/kg
- ApoE ε4 Carrier status

Magnitude, consistency, and duration of dosing important for clinical efficacy
Exposure to Aducanumab 10 mg/kg Was Lower in Study 301 Than in Study 302

Studies 301 and 302

**Study 301**
- 24-week titration to reduce incidence of ARIA
- 14 doses of 10 mg/kg as in Study 103
- No dosing: 22%

**Study 302**
- 24-week titration to reduce incidence of ARIA
- 14 doses of 10 mg/kg as in Study 103
- No dosing: 29%

Patients who have had the opportunity to complete week 78 visit by 20 March 2019.
Early Enrolled Patients Had Lower Exposure to 10 mg/kg

Studies 301 and 302

<table>
<thead>
<tr>
<th>Group</th>
<th>Study 301</th>
<th>Study 302</th>
</tr>
</thead>
<tbody>
<tr>
<td>First 200 patients</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Patients 201-400</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td>Patients 401-600</td>
<td>10</td>
<td>11</td>
</tr>
<tr>
<td>Patients 601-800</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>Patients &gt;800</td>
<td>13</td>
<td>14</td>
</tr>
</tbody>
</table>

Patients who have had the opportunity to complete week 78 visit by 20 March 2019.
CDR-SB Results in Subgroups Created by Stratified Randomization in Which Patients Had the Opportunity for 14 Doses of 10 mg/kg

Study 301
- Post-PV4, ApoE+ (N=58, n=48)
- Pre-PV4, ApoE- (N=78, n=66)
- Post-PV4, ApoE- (N=25, n=23)
  - Weighted mean (N=161, n=137)

Study 302
- Post-PV4, ApoE+ (N=65, n=56)
- Pre-PV4, ApoE- (N=84, n=75)
- Post-PV4, ApoE- (N=31, n=29)
  - Weighted mean (N=180, n=160)

Week 78
- Mean cum dose (mg/kg)
- Median cum dose (mg/kg)
- % diff vs pbo

N: number at baseline. n: number at Week 78.

Patients who have had the opportunity to complete week 78 visit by 20 March 2019.
Distribution of CDR-SB Changes Include a Small Number of Especially Rapidly Progressing Patients

Studies 301 and 302

- Rapidly progressing patient population was evident in all clinical endpoints
- Rapidly progressing patients did not differ in demographics, baseline disease characteristics, comorbidities, concomitant meds, exposure, or incidence of adverse events
- Review of literature and epidemiologic studies were consistent with these findings

Histogram displays data pooled from all three treatment groups from both studies.
Excluding Rapid Progressors Had the Greatest Impact on CDR-SB in Study 301 High-Dose Group

Studies 301 and 302

<table>
<thead>
<tr>
<th>Study</th>
<th>Rapid progressors, n</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>302</td>
</tr>
<tr>
<td>Placebo</td>
<td>4</td>
</tr>
<tr>
<td>low</td>
<td>4</td>
</tr>
<tr>
<td>high</td>
<td>5</td>
</tr>
</tbody>
</table>

- 301 low primary (N=547)
- 301 low excl rap (N=542)
- 302 low primary (N=543)
- 302 low excl rap (N=539)
- 301 high primary (N=555)
- 301 high excl rap (N=546)
- 302 high primary (N=547)
- 302 high excl rap (N=542)

Week 78
Favors aducanumab
Favors placebo
Study 301 Is Sufficiently Understood, and Does not Detract From the Persuasiveness of Study 302

- Study 301 high-dose arm clinical outcome was impacted by lower exposure to the target dose of 10 mg/kg
- Study 301 high-dose arm was affected by imbalance in a small number of rapidly progressing patients
- Patients in Study 301 who had the opportunity for 14 doses of 10 mg/kg had clinical efficacy consistent with Study 302
- Underlying pharmacology of aducanumab is similar in Studies 301 and 302
## Establishing the Substantial Effectiveness of Aducanumab

<table>
<thead>
<tr>
<th>Study</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study 302</td>
<td>A positive study with robust and internally consistent results</td>
</tr>
<tr>
<td>Study 103</td>
<td>An independent, second study providing supportive evidence</td>
</tr>
<tr>
<td>Study 301</td>
<td>A failed study with reasons for difference between studies in results understood and post hoc subgroups supportive of Study 302 and 103</td>
</tr>
</tbody>
</table>

Consistent exposure to 10 mg/kg aducanumab is effective at reducing the clinical decline in patients with early symptomatic Alzheimer’s disease
Safety
Karen Smirnakis, MD, PhD, MPH
Vice President, Head of Global Medical Safety
Biogen
## Summary of Aducanumab Exposure and Follow-up

<table>
<thead>
<tr>
<th>Placebo-controlled period of studies 301 and 302</th>
<th>Aducanumab 10 mg/kg</th>
<th>Total aducanumab (all doses combined)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number dosed</td>
<td>1033</td>
<td>2198</td>
</tr>
<tr>
<td>Exposure, person-years</td>
<td>1295</td>
<td>2752</td>
</tr>
<tr>
<td>Follow-up, person-years</td>
<td>1479</td>
<td>3136</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Combined placebo and long-term extension periods of multiple dose studies(^a)</th>
<th>Aducanumab 10 mg/kg</th>
<th>Total aducanumab (all doses combined)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number dosed</td>
<td>1414</td>
<td>2959</td>
</tr>
<tr>
<td>Exposure, person-years</td>
<td>2106</td>
<td>4520</td>
</tr>
<tr>
<td>Follow-up, person-years</td>
<td>2492</td>
<td>5319</td>
</tr>
</tbody>
</table>

\(^a\) Includes Studies 221AD103, 221AD104, 221AD301, and 221AD302. Does not include Study 221AD205.
Pooling Strategy for Integrated Safety Analysis

Study-level treatment arms

Low dose
- 3 mg/kg carrier
- 6 mg/kg noncarrier

High dose
- 6 mg/kg carrier
- 10 mg/kg noncarrier
- 10 mg/kg carrier

Integrated safety dose groups
- 3 mg/kg
- 6 mg/kg
- 10 mg/kg

Carrier and non-carrier status refers to ApoE ε4 allele.
Amyloid-Related Imaging Abnormalities (ARIA)

ARIA refers to radiographic abnormalities observed with anti-Aβ antibodies

- ARIA-Edema (ARIA-E): vasogenic edema or sulcal effusion
- ARIA-Hemorrhage (ARIA-H): brain microhemorrhages or localized superficial siderosis
- May result from increased cerebrovascular permeability as a consequence of antibody binding to deposited amyloid-beta

Summary of Adverse Events (1)
Studies 301 and 302 Placebo-Controlled Period

<table>
<thead>
<tr>
<th></th>
<th>Patients, n (%)</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Aducanumab</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Placebo N=1087</td>
<td>3 mg/kg N=760</td>
<td>6 mg/kg N=405</td>
<td>10 mg/kg N=1033</td>
<td>Total (all doses combined) N=2198</td>
</tr>
<tr>
<td>Adverse events</td>
<td>945 (86.9)</td>
<td>700 (92.1)</td>
<td>347 (85.7)</td>
<td>946 (91.6)</td>
<td>1993 (90.7)</td>
<td></td>
</tr>
<tr>
<td>ARIA-E</td>
<td>29 (2.7)</td>
<td>223 (29.3)</td>
<td>83 (20.5)</td>
<td>362 (35.0)</td>
<td>668 (30.4)</td>
<td></td>
</tr>
<tr>
<td>Serious adverse events</td>
<td>151 (13.9)</td>
<td>105 (13.8)</td>
<td>54 (13.3)</td>
<td>141 (13.6)</td>
<td>300 (13.6)</td>
<td></td>
</tr>
<tr>
<td>Serious ARIA-E</td>
<td>1 (&lt;0.1)</td>
<td>6 (0.8)</td>
<td>3 (0.7)</td>
<td>13 (1.3)</td>
<td>22 (1.0)</td>
<td></td>
</tr>
<tr>
<td>Fatal adverse events</td>
<td>5 (0.5)</td>
<td>3 (0.4)</td>
<td>0</td>
<td>8 (0.8)</td>
<td>11 (0.5)</td>
<td></td>
</tr>
</tbody>
</table>
Summary of Adverse Events (2)
Studies 301 and 302 Placebo-Controlled Period

<table>
<thead>
<tr>
<th>Adverse event severity</th>
<th>Placebo  N=1087</th>
<th>3 mg/kg  N=760</th>
<th>6 mg/kg  N=405</th>
<th>10 mg/kg  N=1033</th>
<th>Total (all doses combined) N=2198</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>445 (40.9)</td>
<td>252 (33.2)</td>
<td>122 (30.1)</td>
<td>331 (32.0)</td>
<td>705 (32.1)</td>
</tr>
<tr>
<td>Moderate</td>
<td>408 (37.5)</td>
<td>328 (43.2)</td>
<td>177 (43.7)</td>
<td>465 (45.0)</td>
<td>970 (44.1)</td>
</tr>
<tr>
<td>Severe</td>
<td>92 (8.5)</td>
<td>120 (15.8)</td>
<td>48 (11.9)</td>
<td>150 (14.5)</td>
<td>318 (14.5)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>AE leading to discontinuation</th>
<th>Placebo  N=1087</th>
<th>3 mg/kg  N=760</th>
<th>6 mg/kg  N=405</th>
<th>10 mg/kg  N=1033</th>
<th>Total (all doses combined) N=2198</th>
</tr>
</thead>
<tbody>
<tr>
<td>Due to ARIA*</td>
<td>6 (0.6)</td>
<td>47 (6.2)</td>
<td>21 (5.4)</td>
<td>64 (6.2)</td>
<td>132 (6.1)</td>
</tr>
</tbody>
</table>

* Percentages for this row based on the number of patients with at least one postbaseline MRI.
## Adverse Events with ≥5% Incidence in Aducanumab 10 mg/kg ≥2% Difference From Placebo

Studies 301 and 302 Placebo-Controlled Period

<table>
<thead>
<tr>
<th>Adverse events</th>
<th>Placebo N=1087</th>
<th>Aducanumab 10 mg/kg N=1033</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patients, n (%)</td>
<td></td>
</tr>
<tr>
<td>ARIA-E</td>
<td>29 (2.7)</td>
<td>362 (35.0)</td>
</tr>
<tr>
<td>Headache</td>
<td>165 (15.2)</td>
<td>212 (20.5)</td>
</tr>
<tr>
<td>ARIA-H Brain microhemorrhage</td>
<td>71 (6.5)</td>
<td>197 (19.1)</td>
</tr>
<tr>
<td>Fall</td>
<td>128 (11.8)</td>
<td>155 (15.0)</td>
</tr>
<tr>
<td>ARIA-H Superficial siderosis</td>
<td>24 (2.2)</td>
<td>151 (14.6)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>74 (6.8)</td>
<td>92 (8.9)</td>
</tr>
</tbody>
</table>
ARIA Risk Minimization
Dose Titration and MRI Monitoring

Baseline MRI
10 mg/kg
6 mg/kg
3 mg/kg
1 mg/kg

Study Visit
0  4  8  12  16  20  24  28  32  36  40  44  48  52  56  60  64  68  72  76  80

Study week

Post baseline MRI
1  2  3  4  5  6  7  8

14  22  30  42  54  66  78
ARIA Dosing Management

ARIA detected in routine MRI

Mild ARIA
- Continue dosing if asymptomatic, otherwise suspend

Moderate or severe ARIA
- Temporarily suspend dosing until ARIA resolution

Permanently discontinue dosing with severe ARIA-H
# ARIA-E Incidence

**Studies 301 and 302 Placebo-Controlled Period**

<table>
<thead>
<tr>
<th></th>
<th>Placebo N=1076</th>
<th>Aducanumab 10 mg/kg N=1029</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARIA-E</td>
<td>29 (2.7)</td>
<td>362 (35.2)</td>
</tr>
<tr>
<td>ApoE ε4 carriers</td>
<td>16/742 (2.2)</td>
<td>290/674 (43.0)</td>
</tr>
<tr>
<td>ApoE ε4 non-carriers</td>
<td>13/334 (3.9)</td>
<td>72/355 (20.3)</td>
</tr>
</tbody>
</table>

*a Analyses specific to ARIA are based on patients with at least 1 post-baseline MRI.*
Kaplan-Meier Analysis of Time to First ARIA-E
Studies 301 and 302, 10 mg/kg

Placebo-controlled period

Long-term extension

MRI 1 2 3 4 5 6 7
Continued MRI monitoring

Patients at risk, n 1029 938 738 643 537 393 290 195 128 76 32 9 1 0

Time on study (weeks)
98% of ARIA-E events resolved on study
- 69% resolved within 12 weeks
- 83% resolved within 16 weeks

ARIA-E detected in brain MRI (N=362)

- Mild ARIA-E: 109 (30%)
- Moderate ARIA-E: 209 (58%)
- Severe ARIA-E: 44 (12%)

* Each participant counted once, at maximum radiographic severity.
Symptomatic ARIA-E
Studies 301 and 302 Placebo-Controlled Period

- The most common symptoms were headache, confusion, dizziness, and nausea
- Most symptoms during ARIA were mild (67.7%) or moderate (28.3%) in clinical severity
- Severe symptoms were uncommon and included rare reports of seizures

<table>
<thead>
<tr>
<th>Patients with ARIA-E</th>
<th>Placebo (N=1076)</th>
<th>Aducanumab 10 mg/kg (N=1029)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptomatic</td>
<td>26 (89.7)</td>
<td>268 (74.0)</td>
</tr>
<tr>
<td>Symptomatic</td>
<td>3 (10.3)</td>
<td>94 (26.0)</td>
</tr>
</tbody>
</table>

Each participant counted once, at maximum symptomatic status and severity.
ARIA-H Incidence
Studies 301 and 302 Placebo-Controlled Period

<table>
<thead>
<tr>
<th></th>
<th>Patients, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo N=1076</td>
</tr>
<tr>
<td>ARIA-H</td>
<td>94 (8.7)</td>
</tr>
<tr>
<td>Brain microhemorrhage</td>
<td>71 (6.6)</td>
</tr>
<tr>
<td>Localized superficial siderosis</td>
<td>24 (2.2)</td>
</tr>
<tr>
<td>Macrohemorrhage</td>
<td>4 (0.4)</td>
</tr>
</tbody>
</table>
### Relationship Between ARIA-E and ARIA-H

**Studies 301 and 302 Placebo-Controlled Period**

<table>
<thead>
<tr>
<th>Patients, n (%)</th>
<th>Placebo N=1076</th>
<th>Aducanumab 10 mg/kg N=1029</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with ARIA-E</td>
<td>29</td>
<td>362</td>
</tr>
<tr>
<td>ARIA-H subtype</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brain microhemorrhage</td>
<td>4 (13.8)</td>
<td>146 (40.3)</td>
</tr>
<tr>
<td>Localized superficial siderosis</td>
<td>9 (31.0)</td>
<td>140 (38.7)</td>
</tr>
<tr>
<td>Patients without ARIA-E</td>
<td>1047</td>
<td>667</td>
</tr>
<tr>
<td>ARIA-H subtype</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brain microhemorrhage</td>
<td>67 (6.4)</td>
<td>51 (7.6)</td>
</tr>
<tr>
<td>Localized superficial siderosis</td>
<td>15 (1.4)</td>
<td>11 (1.6)</td>
</tr>
</tbody>
</table>
Other Safety Areas of Interest

Compared with placebo, there were no notable differences in the aducanumab group in the incidence of

- Abnormal vital signs
- EKG abnormalities
- Laboratory abnormalities
- Results of the Columbia suicide severity rating scale
- Immunogenicity

Serious hypersensitivity reactions associated with aducanumab infusion were rare, with an incidence of less than 0.1%
Aducanumab Safety Summary

- Safety profile of aducanumab is well characterized
  - More than 5300 person-years of follow-up for aducanumab-treated patients

- ARIA-E is most common AE among aducanumab-treated patients
  - Mainly mild or moderate MRI severity and transient
  - Asymptomatic in majority of patients
  - Majority remained on treatment or resumed treatment after temporary suspension
  - Risk can be mitigated with routine MRI monitoring and dosing management

- Other AEs more common with aducanumab included headache, brain microhemorrhage, falls, superficial siderosis, and diarrhea
Safety Data Collection and Risk Evaluation Will Continue in Post-marketing Setting

Safety Data Collection
- Safety surveillance
- Ongoing long-term clinical study

ARIA Risk Minimization and Management
- Dose titration
- MRI monitoring
- Dose suspension
- Education of prescribers, radiologists, patients and caregivers
Clinical Perspective

Anton P. Porsteinsson, MD
University of Rochester Medical Center
Core Symptoms Measured in Aducanumab Studies

- Cognition: MMSE, ADAS-Cog13
- Function: ADCS-ADL-MCI
- Behavior: Neuropsychiatric Index -10 (NPI-10)

CDR-SB
Clinical Dementia Rating Scale–Sum of Boxes

- Global scale to address disease progression in dementia
- Interviews study partner and patient
- Completed by an independent expert clinician
- Inherently clinically meaningful
High-Dose Aducanumab Reduced Progression in All 6 Domains Measured by CDR-SB

- **Memory**: -28% reduction in decline
- **Orientation**: -24% reduction in decline
- **Judgment and Problem Solving**: -25% reduction in decline
- **Community Affairs**: -23% reduction in decline
- **Home and Hobbies**: -24% reduction in decline
- **Personal Care**: -15% reduction in decline

Reference Source: CDR-SB Table/ explanation of measures
Aducanumab Impacts Multiple Dimensions of AD
Study 302

Outcomes at Week 78 versus placebo

**CDR-SB**

*Primary Endpoint*
22% relative reduction in decline from baseline in the Clinical Dementia Rating Scale–Sum of Boxes (CDR-SB)

*Secondary Endpoints (Cognition)*
MMSE: 18% relative reduction
ADAS Cog: 27% relative reduction

**ADCS-ADL-MCI**

*Secondary Endpoint*
40% relative reduction in decline in AD Cooperative Study-Activities of Daily Living Inventory Study Activities of Daily Living Inventory Mild Cognitive Impairment Version

**NPI-10**

*Exploratory Endpoint*
87% relative reduction in decline the Neuropsychiatric Inventory-10
Overall Safety and Tolerability of Aducanumab

- Remarkably low drop-out rate and highly committed patients
- Minimal differences in AEs and SAEs outside of ARIA
- Good understanding and clear guidelines for managing ARIA
- Risks are manageable: Physicians are highly confident in managing infused biologics, and management strategies are generalizable to large group of providers
Why Do We Need Aducanumab as a Therapy for Alzheimer's Disease?

• Early diagnosis and treatment are feasible
• There is an urgent unmet medical need for treatments that slow or stop the decline

• Aducanumab:
  – Clearly impacts underlying disease pathology
  – Preserves cognitive and functional abilities
  – Reduces behavioral decline
  – Disease-modifying