Understanding Payer Evidentiary Needs for Alzheimer’s Disease Monoclonal Antibody Treatments

July 14, 2021
Welcome and Overview

Mark McClellan
Director, Duke-Margolis Center for Health Policy
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- Research & development plans
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- Any other confidential business information that could be used to reduce competition
Agenda

10:00  Welcome and Framing the Issues
10:20  Session I: Current Landscape of mAb Development for AD and Potential Implications for Coverage and Access
12:10  Lunch
12:40  Session II: Opportunities for Generating Clinical Evidence for Promising AD mAb Treatments
2:10  Break
2:30  Session III: Looking Forward
3:45  Closing Remarks
Introductions
Framing the Issues

Mark McClellan
Duke-Margolis Center for Health Policy
Background

- Drugs targeting beta amyloid (e.g. aducanumab), which many scientists believe is the primary cause of AD, have been in development and reported some promising results.
- Current clinical trials focus on patients with earlier stages of AD, and labeling for aducanumab notes that treatment should be initiated in patients with mild cognitive impairment or mild dementia stage of disease.
- Different stakeholders have differing perspectives on how AD treatments should be valued and priced: ICER's pricing suggestion vs. patient advocates’ assessments.
- Additional evidence on amyloid-busting therapeutics is critical for coverage, payment, and appropriate use decisions.
Remaining Evidentiary Questions

• What is the treatment impact in each stage of the disease and across different types of patients, especially those who have progressed beyond the early stages of AD?

• How can endpoint validation, including surrogate endpoints, potentially be expedited through assessing evidence being developed in the other drug trials or post-market studies?

• How certain is the evidence on how CDR-SB progression translates into additional months of independent living or other key aspects of quality of life?

• Should treatment be continued indefinitely, or is a fixed period adequate (e.g., a year), or should duration be based on resolution of plaques?
  • Are there any long-term safety issues associated with chronic use of the mAb therapies?

• What do appropriate care models for these drugs look like?
  • Will they require monitoring by specialized memory clinics, which have only limited availability today?
  • Will blood tests currently in development reduce the cost and burden of determining treatment eligibility and monitoring disease progression?
Potential Next Steps for CMS

• CMS is a primary payer for the AD mAb population
• CMS’s coverage decision is critical for both FFS Medicare and MA, and will also influence decisions by commercial payers and potentially state Medicaid plans
• CMS opened a NCD process for aducanumab and the broader mAb treatment class on July 12
• In making a NCD, CMS could:
  • Elect to deny coverage for the treatment (unprecedented for Part B drugs)
  • Limit coverage to certain populations
  • Make coverage determinations contingent upon the collection of additional data with the goal of developing more evidence on the drug’s safety and efficacy for beneficiaries (CED)
• There is a set of issues associated with a CED approach, incl. designing randomized trials and/or obtaining convincing evidence from registries
Potential Next Steps for Other Payers

- Private payer actions will be influenced by CMS actions and will likely use the eligibility criteria from the clinical trials, reflecting current FDA labeling, while monitoring results from the other studies underway to further adjust coverage.

- Payers are likely to focus on evidence demonstrating:
  - The relationship between the treatment’s surrogate endpoints as shown in the clinical trials to actual cognitive outcome endpoints.
  - That these outcomes are associated with the reduction of short and long-term costs of care, a better quality of life and decreased caregiver burden and;
  - More efficient care models.

- Payers are also focused on appropriate payment amounts based on assessments of treatment value based on current and emerging evidence.
Topics to Consider Today

• Key issues that payers are facing in making coverage and payment decisions involving the AD mAb drug class;

• Payers’ activities to review the evidence relevant to these decisions, and their initial assessment of the evidence as it is available;

• Top areas where further evidence is needed to address stakeholder needs, and whether studies in progress are likely to be adequate to address these topics; and

• Opportunities for expanding the evidence base on mAb treatments for AD to incorporate payer perspectives.
Session I: Current Landscape of mAb Development for AD and Potential Implications for Coverage and Access
Jeff Cummings
University of Nevada Las Vegas
2021 Alzheimer’s Pipeline

126 agents in Clinical Trials
- Phase 3 – 28
- Phase 2 – 74
- Phase 1 – 24
- DMTs – 104 (83% of agents)
- Biologics – 31
- Small molecule DMTs – 73
- Repurposed – 50 (40% of agents)
- Cog enhancer – 13
- NPS treatment – 9

### Biomarkers used as outcome measures in current Phase 2 and Phase 3 DMT trials

<table>
<thead>
<tr>
<th>Biomarker role in trial</th>
<th>N of trials (%)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Phase 3 DMTs</td>
<td>Phase 2 DMTs</td>
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<tr>
<td>Biomarker as an outcome measure</td>
<td></td>
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<tr>
<td>CSF amyloid</td>
<td>15 (25%)</td>
<td>10 (48%)</td>
<td></td>
</tr>
<tr>
<td>CSF tau</td>
<td>17 (28%)</td>
<td>9 (43%)</td>
<td></td>
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<tr>
<td>FDG-PET</td>
<td>7 (11%)</td>
<td>1 (5%)</td>
<td></td>
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<tr>
<td>vMRI</td>
<td>8 (13%)</td>
<td>8 (38%)</td>
<td></td>
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<tr>
<td>Plasma amyloid</td>
<td>7 (11%)</td>
<td>2 (10%)</td>
<td></td>
</tr>
<tr>
<td>Plasma tau</td>
<td>2 (3%)</td>
<td>1 (5%)</td>
<td></td>
</tr>
<tr>
<td>Amyloid PET</td>
<td>5 (8%)</td>
<td>7 (33%)</td>
<td></td>
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<tr>
<td>Tau PET</td>
<td>4 (7%)</td>
<td>3 (14%)</td>
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<tr>
<td>Biomarker as an entry criterion</td>
<td></td>
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<tr>
<td>Amyloid PET</td>
<td>4 (17%)</td>
<td>11 (14%)</td>
<td></td>
</tr>
<tr>
<td>CSF amyloid</td>
<td>1 (4%)</td>
<td>9 (12%)</td>
<td></td>
</tr>
<tr>
<td>Amyloid PET or CSF amyloid</td>
<td>6 (25%)</td>
<td>11 (14%)</td>
<td></td>
</tr>
<tr>
<td>Tau PET</td>
<td>0</td>
<td>2 (3%)</td>
<td></td>
</tr>
<tr>
<td>CSF amyloid or CSF tau</td>
<td>0</td>
<td>2 (3%)</td>
<td></td>
</tr>
<tr>
<td>Amyloid PET or CSF tau</td>
<td>0</td>
<td>1 (1%)</td>
<td></td>
</tr>
</tbody>
</table>

Mark Mintun

Eli Lilly and Company
Donanemab slows progression of early symptomatic Alzheimer’s disease in Phase 2 proof of concept trial

Mark A. Mintun, Albert C. Lo, Cynthia Duggan Evans, Paul A. Ardayfio, Scott W. Andersen, Sergey Shcherbinin, Jeffrey L. Dage, Ming Lu, Emily C. Collins, John R. Sims, Miroslaw Brys, Daniel M. Skovronsky

Eli Lilly and Company, Indianapolis, IN, USA
**TRAILBLAZER-ALZ**

- Phase 2 registration quality trial to evaluate safety, tolerability and efficacy of donanemab
- Multi-center (56 sites across the United States and Canada), randomized, double-blind, placebo-controlled
- Study population
  - Women and men, 60-85 years of age, with *early symptomatic AD* (combination of prodromal AD [mild cognitive impairment-AD] and mild AD dementia)
  - Screening procedures included Mini–Mental State Examination (MMSE), flortaucipir F18 Positron Emission Tomography (PET) scan, florbetapir F18 PET scan, and magnetic resonance imaging
- Pre-specified statistical analysis plan and independent data-monitoring committee
- Unique features
  - Tau threshold screening
  - Combination arm with donanemab and BACE inhibitor (discontinued with 15 patients enrolled)
  - Short titration phase to full dose aiming to achieve rapid amyloid plaque removal

*NCT03367403*
First study to screen and enroll patients based on their tau pathology

Removes those hypothesized as unlikely to have significant decline in 18 months

No/very low tau

Intermediate tau

High tau

Removes those hypothesized as too advanced to be slowed by anti-amyloid therapy

TAU PET INCLUSION WINDOW

No/very low tau

Intermediate tau

High tau

SUVr = Standardized Uptake Value ratio. *Visual interpretation also done and took precedent when highly discordant.
Study designed to achieve amyloid clearance and then stop dosing

- **Screening**: One to nine weeks before study treatment start. n = 1955
  - Donanemab 700mg Q4W (3 doses) → Donanemab 1400mg Q4W → Donanemab 700mg → Placebo
  - Placebo Q4W

- **Follow up**: Safety assessments

### Notes:
- *At 6-month and 12-month florbetapir PET scans, dosing decision to continue 1400mg Q4W or reduce to 700mg Q4W if amyloid was 11 ≤ CL < 25 or switched to placebo if it was <11 CL at any one measure or 11 ≤ CL < 25 for two consecutive scans.
- 1683 patients excluded due to: screen fail (1563), withdrawal by patient (96), caregiver circumstance (6), and other (18); 15 patients were randomized to discontinued combo.
- One patient was randomized to placebo but discontinued the study before receiving an infusion.

**Abbreviations:**
- CL = Centiloids
- IV = Intravenous
- n = Number of patients
- PET = Positron Emission Tomography
- Q4W = Every 4 weeks

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Secondary outcomes: amyloid lowering

Treatment with donanemab reduced amyloid plaque by 85 Centiloids at 76 weeks compared with placebo.

LS Mean Change $\Delta$ (SE)
Donanemab vs. Placebo

<table>
<thead>
<tr>
<th></th>
<th>LS Mean Change $\Delta$ (SE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>W24</td>
<td>-67.83 (3.16)</td>
</tr>
<tr>
<td>W52</td>
<td>-82.30 (3.41)</td>
</tr>
<tr>
<td>W76</td>
<td>-85.06 (3.87)</td>
</tr>
</tbody>
</table>

40% of donanemab-treated participants reached amyloid negative levels by 24 weeks.

Amyloid negative defined as < 24.1 CL.
# Safety profile

**ARIA-E the most common treatment emergent adverse event**

<table>
<thead>
<tr>
<th>Adverse events (AE)</th>
<th>Placebo (n=125)</th>
<th>Donanemab (n=131)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Participants, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deaths</td>
<td>2 (1.6%)</td>
<td>1 (0.8%)</td>
<td>0.615</td>
</tr>
<tr>
<td>Serious AE</td>
<td>22 (17.6%)</td>
<td>23 (17.6%)</td>
<td>&gt;0.999</td>
</tr>
<tr>
<td>Treatment discontinuations due to AE*</td>
<td>9 (7.2%)</td>
<td>40 (30.5%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Study discontinuations due to AE*</td>
<td>6 (4.8%)</td>
<td>20 (15.3%)</td>
<td>0.007</td>
</tr>
<tr>
<td>Treatment-Emergent AE</td>
<td>113 (90.4%)</td>
<td>119 (90.8%)</td>
<td>&gt;0.999</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment emergent AE ≥5%</th>
<th>Placebo (n=125)</th>
<th>Donanemab (n=131)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Preferred Term, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ARIA-E</td>
<td>1 (0.8%)</td>
<td>35 (26.7%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ARIA-E Symptomatic (subset)</td>
<td>1 (0.8%)</td>
<td>8 (6.1%)</td>
<td></td>
</tr>
<tr>
<td>Fall</td>
<td>19 (15.2%)</td>
<td>17 (13.0%)</td>
<td>0.720</td>
</tr>
<tr>
<td>Dizziness</td>
<td>15 (12.0%)</td>
<td>11 (8.4%)</td>
<td>0.410</td>
</tr>
<tr>
<td>Headache</td>
<td>15 (12.0%)</td>
<td>10 (7.6%)</td>
<td>0.294</td>
</tr>
<tr>
<td>Superficial siderosis of central nervous system</td>
<td>4 (3.2%)</td>
<td>18 (13.7%)</td>
<td>0.003</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>10 (8.0%)</td>
<td>10 (7.6%)</td>
<td>&gt;0.999</td>
</tr>
<tr>
<td>Nausea</td>
<td>4 (3.2%)</td>
<td>14 (10.7%)</td>
<td>0.026</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>9 (7.2%)</td>
<td>9 (6.9%)</td>
<td>&gt;0.999</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>5 (4.0%)</td>
<td>13 (9.9%)</td>
<td>0.086</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>5 (4.0%)</td>
<td>11 (8.4%)</td>
<td>0.198</td>
</tr>
<tr>
<td>ARIA-H</td>
<td>4 (3.2%)</td>
<td>11 (8.4%)</td>
<td>0.109</td>
</tr>
<tr>
<td>Cerebral microhaemorrhage</td>
<td>3 (2.4%)</td>
<td>10 (7.6%)</td>
<td>0.085</td>
</tr>
<tr>
<td>Infusion Related Reaction</td>
<td>0</td>
<td>10 (7.6%)</td>
<td>0.002</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>5 (4.0%)</td>
<td>7 (5.3%)</td>
<td>0.770</td>
</tr>
<tr>
<td>Depression</td>
<td>8 (6.4%)</td>
<td>6 (4.6%)</td>
<td>0.590</td>
</tr>
<tr>
<td>Contusion</td>
<td>10 (8.0%)</td>
<td>0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Vomiting</td>
<td>3 (2.4%)</td>
<td>7 (5.3%)</td>
<td>0.335</td>
</tr>
<tr>
<td>Anxiety</td>
<td>2 (1.6%)</td>
<td>7 (5.3%)</td>
<td>0.173</td>
</tr>
</tbody>
</table>

ARIA-E = Amyloid-Related Imaging Abnormalities-Edema/Effusions
*Discontinued treatment due to protocol-defined criteria and patient/principal investigator-cited reasons for discontinuation.
Primary outcome showed treatment with donanemab significantly slowed disease progression by 32% on iADRS at 76 weeks, compared with placebo.

**Primary Outcome: iADRS**

Composite measure combining the ADAS-Cog₁₃ and the ADCS-iADL, to assess cognition and function, respectively.

32% slowing by donanemab at 76 weeks

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**LS mean change from baseline, SE, 95% CI and p-value are derived using MMRM with factors for treatment, visit, treatment-by-visit interaction, pooled investigator, AChEI and/or memantine use at baseline, and covariates for baseline score, age at baseline, and baseline score-by-visit interaction.**
Donanemab consistently slowed cognitive and functional decline on all secondary clinical endpoints at multiple timepoints compared with placebo.

**iADRS – Primary Outcome**

- **Placebo** n=120
- **Donanemab** n=125

<table>
<thead>
<tr>
<th>Weeks</th>
<th>LS mean change from baseline (SE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>113</td>
</tr>
<tr>
<td>24</td>
<td>110</td>
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<tr>
<td>36</td>
<td>103</td>
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<td>52</td>
<td>90</td>
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<td>64</td>
<td>90</td>
</tr>
<tr>
<td>76</td>
<td>91</td>
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</table>

**Worsening**

- 32% slowing

**CDR-SB**

- **Placebo** n=120
- **Donanemab** n=125

<table>
<thead>
<tr>
<th>Weeks</th>
<th>LS mean change from baseline (SE)</th>
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<tbody>
<tr>
<td>12</td>
<td>115</td>
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<tr>
<td>24</td>
<td>111</td>
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<tr>
<td>36</td>
<td>104</td>
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<td>90</td>
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<td>76</td>
<td>89</td>
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**Worsening**

- 23% slowing

**ADAS-Cog13**

- **Placebo** n=125
- **Donanemab** n=121

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<thead>
<tr>
<th>Weeks</th>
<th>LS mean change from baseline (SE)</th>
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<tr>
<td>12</td>
<td>115</td>
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<td>90</td>
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<td>76</td>
<td>91</td>
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**Worsening**

- 39% slowing

**ADCS-iADL**

- **Placebo** n=120
- **Donanemab** n=125

<table>
<thead>
<tr>
<th>Weeks</th>
<th>LS mean change from baseline (SE)</th>
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<tbody>
<tr>
<td>12</td>
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<td>64</td>
<td>89</td>
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<tr>
<td>76</td>
<td>89</td>
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</table>

**Worsening**

- 23% slowing

**MMSE**

- **Placebo** n=115
- **Donanemab** n=121

<table>
<thead>
<tr>
<th>Weeks</th>
<th>LS mean change from baseline (SE)</th>
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<tbody>
<tr>
<td>12</td>
<td>112</td>
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<tr>
<td>24</td>
<td>107</td>
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<tr>
<td>36</td>
<td>101</td>
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<td>52</td>
<td>90</td>
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<td>64</td>
<td>90</td>
</tr>
<tr>
<td>76</td>
<td>89</td>
</tr>
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</table>

**Worsening**

- 21% slowing

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ADAS-Cog13 = Alzheimer’s Disease Assessment Scale - Cognitive subscale; ADCS-iADL = Alzheimer’s Disease Cooperative Study - Activities of Daily Living Inventory; CDR-SB = Clinical Dementia Rating Scale; iADRS = Integrated Alzheimer’s Disease Rating Scale; LS = Least Squares; n = number of patients; MMSE = Mini–Mental State Examination; SE = Standard Error

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Secondary outcomes: DPM analysis

DPM analysis showed slowing in all clinical endpoints relative to placebo and was similar in magnitude with MMRM.

The Disease Progression Model (DPM) assumes a proportional treatment effect relative to placebo, includes diffuse priors and generated a posterior probability distribution of the disease progression ratio.

- MMRM model: at the 18-month endpoint
- Bayesian DPM: over the entire 18 months (95% credible intervals)
Primary measure of Tau\textsuperscript{IQ} Global Tau Load showed no significant change

Exploratory Regional Analysis shows SIGNIFICANT DECREASE IN TAU LOAD

Global Tau Load (Tau\textsuperscript{IQ})

<table>
<thead>
<tr>
<th>Treatment Arm</th>
<th>Baseline Mean (SD)</th>
<th>LS Mean Change from Baseline (SE)</th>
<th>p-value (treatment difference)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Donanemab</td>
<td>0.44 (0.163)</td>
<td>0.09 (0.007)</td>
<td>0.56</td>
</tr>
<tr>
<td>Placebo</td>
<td>0.46 (0.152)</td>
<td>0.10 (0.007)</td>
<td></td>
</tr>
</tbody>
</table>

Regional SUVR with Cerebellar Gray Reference

<table>
<thead>
<tr>
<th>Region</th>
<th>Slowing (%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frontal Lobe</td>
<td>59.1%</td>
<td>0.0020</td>
</tr>
<tr>
<td>Occipital Lobe</td>
<td>21.0%</td>
<td>0.2036</td>
</tr>
<tr>
<td>Parietal Lobe</td>
<td>44.6%</td>
<td>0.0024</td>
</tr>
<tr>
<td>Mesial Temp. Lobe</td>
<td>NA</td>
<td>0.0459</td>
</tr>
<tr>
<td>Lateral Temp. Lobe</td>
<td>31.8%</td>
<td>0.0328</td>
</tr>
</tbody>
</table>

LS = Least Squares; SD = standard deviation; SE = Standard Error; SUV\textsubscript{r} = Standardized Uptake Value ratio

\#AAL Regions using posterior cerebellum gray matter reference region

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Exploratory analysis of iADRS of enrolled patients by baseline tau PET levels

Intermediate tau enrolled patients were further stratified into terciles by baseline tau PET

Lower baseline tau

Middle baseline tau

Upper baseline tau

Stratified by baseline flortaucipir SUVr; lower third cut point is 1.144; upper third cut point 1.274

iADRS = Integrated Alzheimer’s Disease Rating Scale; LS = Least Squares; n = number of patients; PET = positron emission tomography; SE = Standard Error

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Ongoing/Future Studies

- The pivotal TRAILBLAZER-ALZ2 (NCT04437511) study is ongoing and will continue to test donanemab in a larger study and broader geographic footprint.

- TRAILBLAZER-EXT, a follow-on study for those who participated in TRAILBLAZER-ALZ, is currently enrolling participants (NCT04640077).
Sheila Seleri
Roche/Genetech
GENENTECH AND ROCHE IN ALZHEIMER’S DISEASE

Sheila Seleri, MD, PhD
Group Medical Director, US Medical Affairs
M-US-00011641
OUR INVESTIGATIONAL THERAPEUTICS SPAN DIFFERENT TARGETS, TYPES AND STAGES OF ALZHEIMER’S DISEASE

Crenezumab<sup>1–3</sup>
- Fully human anti-Aβ IgG1 mAb
- Designed to target aggregated Aβ forms – binds oligomers and plaques
- Ongoing study in ADAD only

Semorinemab<sup>3,4–6</sup>
- Anti-tau mAb
- Designed to target extracellular tau, including toxic soluble tau
- LAURIET ongoing in moderate AD

Gantenerumab<sup>3,7–9</sup>
- Fully human anti-Aβ IgG1 mAb
- Designed to target aggregated Aβ forms – binds oligomers and plaques
- Phase 3 GRADUATE program ongoing

Brain shuttle gantenerumab<sup>10–11</sup>
Brain shuttle technology is designed to optimize the penetration of large molecules into the brain

The interaction between Aβ and tau pathology in AD imply that both anti-Aβ and anti-tau therapies are important investigational treatment strategies for people with AD

Gantenerumab, crenezumab, semorinemab and brain shuttle technology are investigational and have not been approved by the FDA. Efficacy and safety have not been established.

Aβ, amyloid beta; AD, Alzheimer’s disease; ADAD, autosomal dominant Alzheimer’s disease; mAb, monoclonal antibody

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Veeva Document Number # M-US-00011641
**GRADUATE I AND II (NCT03444870, NCT03443973) STUDY DESIGN**

<table>
<thead>
<tr>
<th>Day 1</th>
<th>Week 4</th>
<th>Week 8</th>
<th>Week 12</th>
<th>Week 16</th>
<th>Week 20</th>
<th>Week 24</th>
<th>Week 28</th>
<th>Week 32</th>
<th>Week 36 onwards</th>
<th>Week 116b</th>
<th>1020 mg(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>120 mg</td>
<td>255 mg</td>
<td>510 mg</td>
<td>(1020 \text{ mg}^a)</td>
<td>(1020 \text{ mg}^a)</td>
<td>(1020 \text{ mg}^a)</td>
<td>(1020 \text{ mg}^a)</td>
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<td>(1020 \text{ mg}^a)</td>
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</tbody>
</table>

**Main GRADUATE double-blind study**
- SC gantenerumab dose escalation for 9 months followed by gantenerumab at target dose until primary analysis at Week 116\(^b\)
- SC placebo as scheduled until primary analysis at Week 116\(^b\)

**Universal titration**
- Option for home administration
- Optimised manufacturing process for 1020 mg dose

**Post–double-blind period**
- 1-year follow-up or optional enrolment in open-label extension study

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Gantenerumab is investigational and has not been approved by the FDA. Efficacy and safety have not been established.

\(^a\)1020 mg new drug formulation is similarly bioavailable as 1200 mg of the previous drug formulation. \(^b\)GRADUATE studies could be extended to 30 months in total, in the event that COVID-19-related interruptions in dosing and other study procedures worsen significantly.

OLE, open-label extension; SC, subcutaneous.

Ivana Rubino

Biogen
Lynn Kramer

Eisai
Neurodegenerative Disease Pipeline

Eisai Co., Ltd.
July 14, 2021
## Clinical Stage Pipeline Based on AD Continuum and ATN+

<table>
<thead>
<tr>
<th></th>
<th>Preclinical AD</th>
<th>Early AD</th>
<th>AD</th>
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<tr>
<td></td>
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<td>Moderate AD</td>
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<tr>
<td>Preclinical AD</td>
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<td>A3</td>
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<td>A45</td>
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<td>Early AD</td>
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<tr>
<td>MCI due to AD</td>
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<tr>
<td>Mild AD</td>
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<tr>
<td>AD</td>
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<td>Moderate AD</td>
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<tr>
<td>Severe AD</td>
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</tbody>
</table>

### Amyloid aggregates
- **Aducanumab**
  - Anti-Aβ antibody
- **Lecanemab**
  - Anti-Aβ protofibrils antibody

### Tauopathy
- **E2814**
  - Anti-MTBR4 tau antibody
  - Phase I studies ongoing

### Synaptic dysfunction
- **E2511**
  - Synapse regenerant
  - Phase I study initiated

### Dementia with Lewy bodies
- **E2027**
  - PDE9 inhibitor
  - Phase II study ongoing

### Implement drug creation based on hypothesis of novel pathophysiology

Conduct clinical research making full use of biomarkers

---

All projects are investigational. *1: Co-development with Biogen *2: Generic name for BAN2401, an investigational antibody for Alzheimer's disease produced as the result of a strategic research alliance between Eisai and BioArctic *3: Co-research with University College London (UCL), UK *4: microtubule binding region
Open Discussion
Discussion Questions

• What are potentially achievable outcomes that payers will look for in AD mAb treatments? Based on currently available information about the drug class, as well as your own organizations’ early review of this information, what are the highest priority questions where more evidence would be needed to inform coverage decisions?

Specific questions to consider include:

• For which populations might these treatments offer the greatest impact or value?
• What are the most effective ways to improve understanding of the relationship between the treatment’s surrogate endpoints and cognitive outcome endpoints? The relationship between the cognitive outcomes to other measures of value, such as quality of life, independence and reduced supportive care costs and caregiver burden?
• What are the expectations associated with differing durations of treatment?
• What are the most effective and efficient care models for mAb treatment, including diagnosis, monitoring, and management of treatment complications?
Discussion Questions

• What coverage and payment decisions might be appropriate for these treatments?
  • How will payers treat populations included in clinical trials versus less-studied populations when making coverage determinations? Would coverage differ by population group?
  • What additional evidence described previously would affect payers’ willingness to cover these drugs?
• What are payers’ pricing and payment expectations with regard to the AD mAb drug class? What is the expected pricing dynamic when there are several similar drugs in this space?
  • How might past experiences in the context of pricing and competition help inform this discussion, for example, the approval of multiple PCSK9 drugs for lowering cholesterol and the competition that impacted hepatitis C treatment prices?
Session II: Opportunities for Generating Clinical Evidence for Promising AD mAb Treatments
Maria Carrillo

The Alzheimer’s Association
George Vradenburg
UsAgainstAlzheimer’s
Open Discussion
Joseph Johnston

Eli Lilly and Company
Jennifer Whiteley

Roche/Genentech
Chris Leibman
Biogen
Amir Tahami

Eisai
Open Discussion
Discussion Questions

• Will the pivotal trials underway now or the planned Phase 4 (postmarket) studies provide substantial insights into the key evidence questions?

• What are near-term ways to augment these studies to fill key evidence gaps?

• Can these key evidence questions be addressed through observational real-world studies (e.g., registries), or are randomized studies needed?

• What potentially feasible further postmarket studies are most important to consider now – for both early-stage and later-stage patients?

• Are there any learnings to leverage from our collective experience with registries, practical platform trials, and other postmarket evidence initiatives?

• What should CMS consider in terms of an evidence development (e.g., CED) approach for these therapies? How might these studies be designed and executed given the existing coverage issues and challenges associated with creating a randomized controlled trial for the treatment?
Session III: Looking Forward
Steve Miller
Cigna
Kate Goodrich
Humana
Open Discussion
Discussion Questions

• How can stakeholders work together to address these questions in both premarket and postmarket studies?
• Would additional public-private collaboration help address these questions?
• What potential payment models could address the health care spending and evidence concerns associated with these therapies?
Closing Remarks

Mark McClellan
Duke-Margolis Center for Health Policy
Thank You!

Contact Us

healthpolicy.duke.edu

Subscribe to our monthly newsletter at dukemargolis@duke.edu

1201 Pennsylvania Avenue, NW, Suite 500
Washington, DC 20004

DC office: 202-621-2800
Durham office: 919-419-2504

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