Lecanemab
Peripheral and Central Nervous System Drugs Advisory Committee
June 9, 2023

Introductory Comments

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Office of Neuroscience
Center for Drug Evaluation and Research
Lecanemab

• Lecanemab (Leqembi) was approved on January 6, 2023, under the accelerated approval pathway

  – LEQEMBI is indicated for the treatment of Alzheimer’s disease. Treatment with LEQEMBI should be initiated in patients with mild cognitive impairment or mild dementia stage of disease, the population in which treatment was initiated in clinical trials. There are no safety or effectiveness data on initiating treatment at earlier or later stages of the disease than were studied. This indication is approved under accelerated approval based on reduction in amyloid beta plaques observed in patients treated with LEQEMBI [see Clinical Studies (14)]. Continued approval for this indication may be contingent upon verification of clinical benefit in a confirmatory trial.
Approval Pathways

• Traditional Approval
  – Substantial evidence of effectiveness demonstrated on a *clinically meaningful* endpoint (e.g., how a patient feels, functions, or survives) or *validated surrogate*
  – Drug is safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling
Approval Pathways

- Accelerated Approval (21 CFR 314.500 - subpart H, accelerated approval regulations)
  - May be considered for serious or life-threatening diseases with an unmet need
  - Substantial evidence of effectiveness demonstrated on an endpoint that is not itself a direct measure of the clinical benefit of interest but is instead reasonably likely to predict that clinical benefit (e.g., surrogate or intermediate clinical endpoint) based on “epidemiologic, therapeutic, pathophysiologic, or other evidence”
  - FDA may require further adequate and well-controlled clinical trials to verify and describe clinical benefit for products approved under accelerated approval in order to obtain traditional approval
Lecanemab Accelerated Approval

• The accelerated approval of lecanemab took into consideration the following:
  – Alzheimer’s disease is a serious or life-threatening diseases with an unmet need
  – Substantial evidence of effectiveness was demonstrated on a surrogate endpoint, reduction in amyloid plaque burden measured by positron emission tomography (PET) imaging, that was determined to be reasonably likely to predict clinical benefit
  – An ongoing/completed Phase 3 randomized, controlled clinical trial that could potentially verify the clinical benefit of lecanemab for the treatment of Alzheimer’s disease (issued as post-marketing requirement (PMR) 4384-1)

• This submission contains results of Study 301 (CLARITY AD) that are intended to fulfill the PMR and verify the clinical benefit of lecanemab for the treatment of Alzheimer’s disease
Study 301 (CLARITY AD)

- An 18-month (78-week) multicenter, randomized, double-blind, placebo-controlled, parallel-group study in patients with mild cognitive impairment due to Alzheimer’s disease (AD) or mild AD dementia
- Randomization to placebo (n=897) or lecanemab 10 mg/kg biweekly (n=898) in a 1:1 ratio
- Statistically significant treatment effects were demonstrated on the primary endpoint and secondary endpoints
  - Primary endpoint: change from baseline in the Clinical Dementia Rating - Sum of Boxes (CDR-SB) at 18 months of treatment
  - Secondary endpoints:
    - Brain amyloid plaque levels as measured by PET
    - Alzheimer’s Disease Assessment Scale – Cognitive Subscale (ADAS-Cog 14),
    - Alzheimer’s Disease Composite Score (ADCOMS)
    - Alzheimer’s Disease Cooperative Study – Activities of Daily Living – Mild Cognitive Impairment (ADCS-ADL-MCI)
Safety of Lecanemab

• Approved prescribing information (PI) for lecanemab includes warnings for:
  – Amyloid-related imaging abnormalities (ARIA)
    • Findings of edema (ARIA-E) or microhemorrhages and superficial siderosis (ARIA-H) on MRI
    • Usually asymptomatic but serious and life-threatening events can occur
  – Infusion-related reactions
• Safety in Study 301 appears to be generally consistent with current approved labeling for lecanemab
Questions for the Advisory Committee

• **Discussion:** Discuss the results from Study 301 (CLARITY AD) and whether they provide evidence of clinical benefit of lecanemab for the treatment of Alzheimer’s disease (AD).

• **Vote:** Do the results of Study 301 (CLARITY AD) verify the clinical benefit of lecanemab for the treatment of AD?

• **Discussion:** Discuss the overall benefit/risk assessment of lecanemab for the treatment of AD. Additionally, consider the following subgroups in your assessment:
  – Apolipoprotein E (ApoE) ε4 homozygotes
  – Patients requiring concomitant treatment with anticoagulant agents
  – Patients with cerebral amyloid angiopathy
Clinical Overview of Efficacy

Kevin M. Krudys, PhD
Clinical Efficacy Reviewer
Associate Director
Office of Neuroscience
Center for Drug Evaluation and Research
Lecanemab

- Lecanemab is an amyloid beta-directed antibody indicated for the treatment of Alzheimer’s disease
  - Received accelerated approval January 6, 2023
- Mechanism of Action:
  - Monoclonal antibody directed against aggregated soluble and insoluble forms of amyloid beta
- Proposed Dosing Regimen
  - 10 mg/kg administered as an IV infusion once every two weeks
Anti-Amyloid Therapies Are Not a Distinct Class

• Previous failures of “anti-amyloid” therapies
  – Inclusion of individuals without evidence of brain amyloid pathology or at later stages of Alzheimer’s disease
  – Insufficient dosing
  – Unknown target engagement
  – Off-target effect
  – Lacking proof-of-concept prior to Phase 3 trials
  – *Did not clear brain amyloid plaque*

• Newer generation of anti-amyloid therapies targeting aggregated amyloid has learned from previous failures

Accumulated evidence has established that robust reduction of brain amyloid plaque is associated with a reduction in clinical decline over 18 months
Clinical Studies Relevant to Evaluation of Efficacy

- **Study 201**
  - Multicenter, randomized, double-blind, placebo-controlled study
  - Primary objectives: dose-regimen determination, safety, and tolerability
  - Observed reduction in brain amyloid plaque supported accelerated approval

- **Study 301 (Clarity AD)**
  - Multicenter, global, randomized, double-blind, placebo-controlled study
  - Primary objective: Efficacy and safety of lecanemab
  - In September 2021, FDA agreed that Study 301 may serve as a confirmatory clinical trial to verify the clinical benefit of lecanemab
Study 301: Trial Design

**N=1795**

Key eligibility criteria:
- MCI due to AD or mild AD dementia
- CDR global score of 0 or 1
- Positive amyloid pathology (PET or CSF)
- MMSE score ≥ 22

Lecanemab (IV infusion) 10 mg/kg biweekly (n=898)

**Open-label Extension (Up to 4 years)**

Open-label lecanemab

Placebo (IV infusion) biweekly (n=897)

Optional Longitudinal Studies:
- Amyloid PET; n=716
- Tau PET; n=257
- CSF biomarkers; n=281

Core Phase (18 months)

Stratification factors:
- Clinical subgroup (MCI or mild AD dementia)
- ApoE ε4 status (carrier or non-carrier)
- Ongoing treatment with AD medications
- Geographic region

**Primary Endpoint:**
- CDR-SB at 18 months

**Secondary Endpoints:**
- Amyloid PET
- ADAS-Cog 14
- ADCOMS
- ADCS-ADL-MCI
  Raters blinded to safety assessment


[www.fda.gov](http://www.fda.gov)
Efficacy Analysis Sets

• EMA/PMDA
  – Full Analysis Set+ (FAS+)
  – Randomized subjects who received at least one dose, have baseline assessment, and at least one post-dose primary efficacy measurement

• FDA/global
  – Full Analysis Set (FAS)
  – Excluded subjects randomized on or before the end date of dosing hold at sites which had dosing holds ≥6 weeks (i.e., 3 consecutive doses)
  – Excludes 68 subjects (42 placebo, 26 lecanemab) from 19 sites who missed ≥3 consecutive doses*

* Correction to FDA Briefing Document

EMA: European Medicines Agency, PMDA: Pharmaceuticals and Medical Devices Agency (Japan)
Study 301 Met Primary Endpoint (CDR-SB)

- Statistically significant reduction in decline (-0.45[-27%], p=0.00005)
- Similar observation in FAS population (-0.39[-25%], p=0.0004)
- Placebo decline of 1.66 over 18 months
- Robust to prespecified sensitivity analyses, including non-normality and potential of functional unblinding due to ARIA or infusion reactions

CDR-SB: Clinical Dementia Rating-Sum of Boxes, FAS: Full Analyses Set, ARIA: amyloid-related imaging abnormalities
### Study 301 Met All Secondary Endpoints

<table>
<thead>
<tr>
<th>Secondary Endpoint</th>
<th>Placebo Decline (N=875)</th>
<th>Lecanemab (N=859)</th>
<th>Difference vs. Placebo (%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Adjusted Mean</td>
<td>n</td>
<td>Adjusted Mean</td>
</tr>
<tr>
<td>ADAS-Cog 14</td>
<td>738</td>
<td>5.58</td>
<td>703</td>
<td>4.14</td>
</tr>
<tr>
<td>ADCS-ADL-MCI</td>
<td>707</td>
<td>-5.50</td>
<td>676</td>
<td>-3.48</td>
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<tr>
<td>ADCOMS</td>
<td>749</td>
<td>0.21</td>
<td>708</td>
<td>0.16</td>
</tr>
</tbody>
</table>

Source: Tables 14.2.2.2.2, 14.2.2.3.2, and 14.2.2.4.2 In Study 301 CSR
FAS+ Population

- Statistically significant reduction in brain amyloid (-59.1 Centiloids, p<0.00001)
- Similar results observed in FAS population

CDR-SB in Homozygous ApoE ε4 Carriers Was Only Subgroup for Which Treatment Contrast Did Not Favor Lecanemab

ApoE: apolipoprotein E, CDR-SB: Clinical Dementia Rating-Sum of Boxes, FAS+ - full analysis set

Longitudinal results for treatment and placebo groups largely overlap
Key Secondary Clinical Endpoints Favored Lecanemab in ApoE ε4 Homozygotes

ADAS-Cog 14

<table>
<thead>
<tr>
<th>ApoE status</th>
<th>n(placebo)/n(lecanemab)</th>
<th>favors lecanemab</th>
<th>favors placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-Carrier</td>
<td>273/266</td>
<td>-3</td>
<td>-4</td>
</tr>
<tr>
<td>Carrier</td>
<td>599/588</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Heterozygote</td>
<td>467/453</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Homozygote</td>
<td>132/135</td>
<td>1.5</td>
<td>2</td>
</tr>
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</table>

ADCS-ADL-MCI

<table>
<thead>
<tr>
<th>ApoE status</th>
<th>n(placebo)/n(lecanemab)</th>
<th>favors lecanemab</th>
<th>favors placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-Carrier</td>
<td>245/234</td>
<td>-3</td>
<td>-4</td>
</tr>
<tr>
<td>Carrier</td>
<td>551/549</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Heterozygote</td>
<td>430/422</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Homozygote</td>
<td>121/127</td>
<td>1.5</td>
<td>2</td>
</tr>
</tbody>
</table>

Similar trends favoring lecanemab were observed for health outcome assessments and biomarkers

Treatment Effect in Homozygous ApoE ε4 Carriers

• No *a priori* expectation for diminished treatment effect in ApoE ε4 carriers or for a different effect in homozygous and heterozygous carriers
• Inconsistent findings in ApoE ε4 carrier subgroups across other therapies in the class
• Stratification was based on ApoE ε4 carrier status (carrier/non-carrier) and not genotype (homozygous/heterozygous)
• Size of homozygous ApoE ε4 carrier subgroup is one of smallest tested in Study 301
• Results for secondary endpoints, health outcome measures, and biomarkers all support treatment effect in homozygous ApoE ε4 carriers
Confirmation of Clinical Benefit of Lecanemab

• Study 301 met primary endpoint, reducing change from baseline on CDR-SB (-0.45, p=0.00005), an integrated scale that meaningfully assesses function and cognition
• Statistically significant treatment effects on all multiplicity-controlled secondary endpoints (amyloid PET, ADAS-Cog 14, ADCOMS, ADCS-ADL-MCI)
• Supported by favorable results across prespecified subgroups
• Biomarkers reflecting target engagement (brain amyloid), downstream tau pathophysiology (tau PET), and neurodegeneration (t-tau) support observations on clinical outcome measures
Statistical Overview

Tristan Massie, PhD
Biostatistics Reviewer
Division of Biostatistics 1
Office of Biostatistics
Center for Drug Evaluation and Research
Analysis Populations

- FAS+: all randomized patients who received at least one dose of study drug and had a baseline assessment and at least one post-baseline CDR-SB assessment
- FDA FAS: subset of FAS+ with pre-specified exclusion of 68 patients at sites closed for 6 or more weeks during peak COVID period in 2020
- Sample size was to be increased by 200 patients to a total of approximately 1766 randomized patients in Dec 2020, due to concerns about missed doses related to the COVID-19 pandemic
Analysis Methods

• Primary analysis: CDR-SB analyzed by a mixed model for repeated measures (MMRM) in the FDA FAS population to compare the treatment group difference at Week 79
  – Covariates used in the MMRM model: baseline score, visit (categorical), baseline score by visit interaction, presence of concomitant AD medications, baseline disease severity (MCI/Mild AD), APOE4 status, region, treatment group, and treatment group-by-visit interactions
  – CDR-SB assessments collected after changes in concomitant AD medications are included
  – Handling of missing data was based on “missing at random” assumption
## Subject Disposition

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Lecanemab 10 mg/kg biweekly</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Randomized</strong></td>
<td>897</td>
<td>898</td>
</tr>
<tr>
<td><strong>FAS+</strong></td>
<td>875</td>
<td>859</td>
</tr>
<tr>
<td><strong>FDA FAS</strong></td>
<td>833</td>
<td>833</td>
</tr>
<tr>
<td><strong>Symptomatic Alzheimer’s medication changes</strong></td>
<td>101 (11.2%)</td>
<td>96 (10.7%)</td>
</tr>
<tr>
<td><strong>Deaths within 79 Weeks</strong></td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td><strong>Missing Week 79 CDR-SB assessment</strong></td>
<td>140 (15.6%)</td>
<td>184 (20.5%)</td>
</tr>
</tbody>
</table>
# Primary Results in FAS+

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Treatment Group</th>
<th>N</th>
<th>Baseline Score</th>
<th>Week 79 LS Mean</th>
<th>PBO-LEC Difference (95% C.I.)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CDR-SB</td>
<td>Placebo</td>
<td>875</td>
<td>3.22</td>
<td>1.66</td>
<td>0.45 (0.23, 0.67)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>Lecanemab</td>
<td>859</td>
<td>3.17</td>
<td>1.21</td>
<td>--</td>
<td></td>
</tr>
</tbody>
</table>

Note: FDA FAS (Covid pandemic related exclusions) and FAS+ population results are consistent.
Change in CDR-SB Over Time in Controlled Phase (FAS+)

Increasing separation over time

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Week 13</th>
<th>Week 27</th>
<th>Week 39</th>
<th>Week 53</th>
<th>Week 65</th>
<th>Week 79</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>675</td>
<td>849</td>
<td>828</td>
<td>813</td>
<td>779</td>
<td>767</td>
<td>757</td>
</tr>
<tr>
<td>Lec 10 mg/kg Biweekly</td>
<td>859</td>
<td>824</td>
<td>798</td>
<td>779</td>
<td>765</td>
<td>738</td>
<td>714</td>
</tr>
</tbody>
</table>
Sensitivity Analyses

- Selected Sensitivity analyses:
  - Tipping point analysis to explore sensitivity to alternative missing not at random assumptions
  - Censoring assessments after initiation/dose adjustment of symptomatic AD drug or treatment discontinuation
  - Censoring assessments after ARIA adverse events
  - With imputation as if control patient for lecanemab arm after study discontinuation due to treatment-related adverse events
  - Full ITT population analysis

- The analyses show that the result of the primary analysis on CDR-SB is reasonably insensitive to the handlings of missing data and intercurrent events
### Key Secondary Endpoint Results

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Treatment Group</th>
<th>N</th>
<th>Baseline score</th>
<th>Week 79 LS Mean</th>
<th>PBO-LEC Difference (95% C.I.)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amyloid PET</td>
<td>Placebo</td>
<td>325</td>
<td>1.4</td>
<td>3.6</td>
<td>59.2 (55.6, 62.7)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td></td>
<td>Lecanemab</td>
<td>342</td>
<td>1.4</td>
<td>-55.5</td>
<td>--</td>
<td></td>
</tr>
<tr>
<td>ADAS-COG-14</td>
<td>Placebo</td>
<td>872</td>
<td>24.4</td>
<td>5.6</td>
<td>1.4 (0.6, 2.3)</td>
<td>0.0007</td>
</tr>
<tr>
<td></td>
<td>Lecanemab</td>
<td>854</td>
<td>24.4</td>
<td>4.2</td>
<td>--</td>
<td></td>
</tr>
<tr>
<td>ADCOMS (x 100)</td>
<td>Placebo</td>
<td>833</td>
<td>39.9</td>
<td>20.9</td>
<td>4.5 (2.2, 6.9)</td>
<td>0.0002</td>
</tr>
<tr>
<td></td>
<td>Lecanemab</td>
<td>831</td>
<td>39.7</td>
<td>16.3</td>
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<td></td>
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<tr>
<td>ADCS-ADL-MCI</td>
<td>Placebo</td>
<td>796</td>
<td>41.1</td>
<td>-5.5</td>
<td>-2.0 (-2.8, -1.2)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td></td>
<td>Lecanemab</td>
<td>783</td>
<td>41.3</td>
<td>-3.5</td>
<td>--</td>
<td></td>
</tr>
</tbody>
</table>

Note: Study 301 satisfied Hierarchical Testing Plan to account for multiplicity.
Summary

• Study 301 provides statistical evidence for lecanemab, based on the results of primary endpoint and key secondary endpoints
  – Week 79 CDR-SB difference 0.45 (95% C.I.= 0.23, 0.67)
    • Difference emerges by Week 27 and increases over time
  – Key secondaries:
    • ADAS-Cog-14 difference: 1.4 (95% C.I.= 0.6, 2.3)
    • ADCOMS difference: 0.05 (95% C.I.=0.02, 0.07)
    • ADCS-ADL-MCI difference: -2.0 (95% C.I. -2.8, -1.2)
• Dr. Erten-Lyons will present the safety data
Clinical Overview of Safety

Deniz Erten-Lyons, MD
Clinical Safety Reviewer
Division of Neurology 1
Office of Neuroscience
Center for Drug Evaluation and Research
Key Safety Issues

- Infusion Related Reactions and Hypersensitivity
- Amyloid Related Imaging Abnormalities (ARIA)
- Cerebral Hemorrhage
## Overview of Safety in Study 301

<table>
<thead>
<tr>
<th></th>
<th>Placebo N=898 n (%)</th>
<th>Lecanemab N=898 n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Deaths</strong>*</td>
<td>7 (0.8)</td>
<td>6 (0.7)</td>
</tr>
<tr>
<td><strong>Treatment Emergent Adverse Events</strong></td>
<td>737 (82)</td>
<td>800 (89)</td>
</tr>
</tbody>
</table>

*Includes deaths for which the precipitating event occurred within 30 days of a dose of lecanemab*
# Most Common Treatment Emergent Adverse Events in Study 301

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Placebo N= 897</th>
<th>Lecanemab N =898</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infusion related reaction</td>
<td>64 (7)</td>
<td>236 (26)</td>
</tr>
<tr>
<td>ARIA-E</td>
<td>15 (2)</td>
<td>113 (13)</td>
</tr>
<tr>
<td>ARIA-H microhemorrhage</td>
<td>69 (8)</td>
<td>126 (14)</td>
</tr>
<tr>
<td>Headache</td>
<td>73 (8)</td>
<td>101 (11)</td>
</tr>
</tbody>
</table>
Amyloid Related Imaging Abnormalities (ARIA)

- Monoclonal antibodies directed against aggregated forms of beta amyloid (Aβ), including lecanemab, can cause ARIA, observed on brain MRI.
- It is hypothesized that anti-Aβ antibodies accelerate breakdown and clearance of Aβ, which may disrupt vascular integrity and result in leakage into surrounding tissues with parenchymal or sulcal changes observed on MRI:
  - ARIA-E (edema): vasogenic edema or sulcal effusion.
  - ARIA-H (hemosiderin deposition): microhemorrhage and superficial siderosis.
ARIA

• ARIA can occur spontaneously in patients with Alzheimer’s disease (AD) or cerebral amyloid angiopathy (CAA).
• ARIA-H and ARIA-E can occur together.
• ARIA is usually asymptomatic, although rarely serious and life-threatening events can occur. When present, reported symptoms associated with ARIA may include headache, confusion, visual changes, dizziness, nausea, gait difficulty, and focal neurologic deficits.
Incidence of ARIA and Cerebral Hemorrhage in Study 301

<table>
<thead>
<tr>
<th></th>
<th>Placebo N=897 n (%)</th>
<th>Lecanemab N=897 n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ARIA</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>84 (9)</td>
<td>191 (21)</td>
</tr>
<tr>
<td>Symptomatic ARIA</td>
<td>2 (0.2)</td>
<td>29 (3)</td>
</tr>
<tr>
<td><strong>ARIA-E</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>15 (2)</td>
<td>113 (13)</td>
</tr>
<tr>
<td><strong>ARIA-H</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isolated ARIA-H</td>
<td>80 (9)</td>
<td>152 (17)</td>
</tr>
<tr>
<td></td>
<td>69 (8)</td>
<td>78 (9)</td>
</tr>
<tr>
<td><strong>ARIA-H microhemorrhage</strong></td>
<td>68 (8)</td>
<td>126 (14)</td>
</tr>
<tr>
<td><strong>ARIA-H superficial siderosis</strong></td>
<td>21 (2)</td>
<td>50 (6)</td>
</tr>
<tr>
<td>Cerebral Hemorrhage*</td>
<td>0 (0)</td>
<td>6 (0.7)</td>
</tr>
</tbody>
</table>

*Cerebral hemorrhage >1cm occurring within 40 days of last dose included*
Incidence of ARIA and Cerebral Hemorrhage by ApoE €4 Status in Study 301

<table>
<thead>
<tr>
<th></th>
<th>Non-Carriers</th>
<th></th>
<th>Heterozygote</th>
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<th>Homozygote</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>Placebo N=286</td>
<td>Lecanemab N=278</td>
<td>Placebo N=478</td>
<td>Lecanemab N=479</td>
<td>Placebo N=133</td>
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<tr>
<td>ARIA</td>
<td></td>
<td>n=286 n (%)</td>
<td>Lecanemab n (%)</td>
<td>Placebo n (%)</td>
<td>Lecanemab n (%)</td>
<td>Placebo n (%)</td>
</tr>
<tr>
<td></td>
<td>11 (4)</td>
<td>37* (13)</td>
<td>44 (9)</td>
<td>91* (19)</td>
<td>29 (22)</td>
<td>63 (45)</td>
</tr>
<tr>
<td>ARIA-E</td>
<td>1 (0.3)</td>
<td>15 (5)</td>
<td>9 (2)</td>
<td>52 (11)</td>
<td>5 (4)</td>
<td>46 (33)</td>
</tr>
<tr>
<td>ARIA-H</td>
<td>11 (4)</td>
<td>32 (12)</td>
<td>41 (9)</td>
<td>66 (14)</td>
<td>28 (21)</td>
<td>54 (38)</td>
</tr>
<tr>
<td>Cerebral Hemorrhage</td>
<td>0</td>
<td>1 (0.4)</td>
<td>0</td>
<td>3 (0.6)</td>
<td>0</td>
<td>2 (1)</td>
</tr>
</tbody>
</table>

* Correction to FDA Briefing Document.
ARIA-H includes microhemorrhages and superficial siderosis, excludes cerebral hemorrhage.
Cerebral hemorrhage>1cm occurring within 40 days of last dose included.
## Incidence of Cerebral Hemorrhage With Antithrombotics in Study 301

<table>
<thead>
<tr>
<th></th>
<th>Cerebral Hemorrhage</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo</td>
</tr>
<tr>
<td><strong>Not on antithrombotic</strong></td>
<td>0/584</td>
</tr>
<tr>
<td><strong>On antithrombotic</strong></td>
<td></td>
</tr>
<tr>
<td>Aspirin ≤81 mg</td>
<td>0/304</td>
</tr>
<tr>
<td>Aspirin ≥81 mg, other</td>
<td>0/144</td>
</tr>
<tr>
<td>antiplatelet or dual antiplatelet</td>
<td>0/107</td>
</tr>
<tr>
<td>Anticoagulation</td>
<td>0/72</td>
</tr>
</tbody>
</table>

Source: Extracted from Eisai Table sBLA IR9-1mod, submitted May 1, 2023, cerebral hemorrhage>1 cm occurring within 40 days of last dose included
Deaths Associated With Cerebral Amyloid Angiopathy (CAA) and Inflammatory Vasculitis in Study 301

- A high burden of CAA and findings consistent with an inflammatory vasculitis were identified on autopsy in 2 deaths in ApoE ε4 homozygotes on lecanemab, both of whom complained of headaches shortly after exposure to lecanemab. An additional death with possible CAA occurred in an ApoE ε3 homozygote with cerebral hemorrhage in the setting of confounding factors including anticoagulant use.

- The inflammatory vasculitis in the 2 cases with a high burden of CAA resembled CAA related inflammation (CAA-ri), a spontaneous inflammatory response to the vascular amyloid deposits which presents with symptoms and imaging findings similar to ARIA-E and ARIA-H. 1,2

- The risk of both severe CAA and CAA-ri is highest in ApoE ε4 homozygotes.1,3

- Up to 90% of patients with AD are reported to have some degree of underlying CAA, but not all show characteristics MRI findings during life.4,5

- Risk of lecanemab use in patients with CAA is not well characterized; the benefit-risk discussion needs to consider the uncertainties with this potential risk.

Safety Summary and Conclusions

• ARIA, cerebral hemorrhage, infusion-related reactions and hypersensitivity are the main safety signals associated with lecanemab.

• Risk of ARIA is higher in ApoE ε4 homozygotes compared to heterozygotes and noncarriers.

• Risk in the presence of CAA, or with antithrombotic use are not well characterized; the benefit-risk discussion needs to consider these uncertainties with the potential risks.

• Risks and uncertainties can be described in prescribing information.

• Prescriber and patient education regarding ARIA, and surveillance for any new or worsening neurological symptoms and follow up with unscheduled MRIs, particularly in ApoE ε4 homozygotes, may mitigate some risks of ARIA associated with lecanemab.
Concluding Remarks

Teresa Buracchio, MD
Director (Acting)
Office of Neuroscience
Center for Drug Evaluation and Research
## Clinical Dementia Rating Scale-sum of boxes

Scored as decline from previous usual level due to cognitive loss, not impairment due to other factors.

<table>
<thead>
<tr>
<th></th>
<th>None</th>
<th>Questionable</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Memory</strong></td>
<td>0</td>
<td>0.5</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>No memory loss or slight inconsistency of forgetfulness</td>
<td>Moderate memory loss; more marked for recent events; defect interferes with everyday activities</td>
<td>Severe memory loss; only highly learned material retained; new material rapidly lost</td>
<td>Severe memory loss; only fragments remain</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fully oriented</td>
<td>Fully oriented except for slight difficulty with time relationships</td>
<td>Moderate difficulty with time relationships; oriented for place at examination; may have geographic disorientation elsewhere</td>
<td>Severe difficulty with time relationships; usually disoriented to time, often to place</td>
<td>Oriented to person only</td>
<td></td>
</tr>
<tr>
<td><strong>Judgment &amp; Problem Solving</strong></td>
<td>Solves everyday problems &amp; handles business &amp; financial affairs well; judgment good in relation to past performance</td>
<td>Slight impairment in solving problems, similarities, and differences</td>
<td>Moderately impaired in handling problems, similarities, and differences; social judgment usually maintained</td>
<td>Severely impaired in handling problems, similarities, and differences; social judgment usually impaired</td>
<td>Unable to make judgments or solve problems</td>
</tr>
<tr>
<td>Independent function at usual level in job, shopping, volunteer and social groups</td>
<td>Slight impairment in these activities</td>
<td>Unable to function independently at these activities although may still be engaged in some; appears normal to casual inspection</td>
<td>No pretense of independent function outside home; appears well enough to be taken to functions outside a family home</td>
<td>Appears too ill to be taken to functions outside a family home</td>
<td></td>
</tr>
<tr>
<td>Life at home, hobbies, and intellectual interests well maintained</td>
<td>Life at home, hobbies, and intellectual interests slightly impaired</td>
<td>Mild but definite impairment of function at home; more difficult chores abandoned; more complicated hobbies and interests abandoned</td>
<td>Only simple chores preserved; very restricted interests, poorly maintained</td>
<td>No significant function in home</td>
<td></td>
</tr>
<tr>
<td>Fully capable of self-care</td>
<td>Needs prompting</td>
<td>Requires assistance in dressing, hygiene, keeping of personal effects</td>
<td>Requires much help with personal care; frequent incontinence</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Source: https://knightadrc.wustl.edu/wp-content/uploads/2021/06/CDR-Table.pdf
Change in CDR-SB Over Time in Controlled Phase (FAS+)

Increasing separation over time

Adjusted mean difference at 18 months: -0.451

27.1% less decline on Lecanemab 10 mg/kg Biweekly at Week 79
Identified risks of ARIA and infusion-related reactions are currently described as Warnings in the lecanemab prescribing information (PI) based on the Phase 2 study.

PI will be updated to incorporate safety information from Study 301.
Apolipoprotein E (ApoE) ε4 homozygotes

ApoE ε4 Carrier Status and Risk of ARIA

In Study 1, 6% (10/161) of patients in the LEQEMBI group were apolipoprotein E ε4 (ApoE ε4) homozygotes, 24% (39/161) were heterozygotes, and 70% (112/161) were noncarriers. The incidence of ARIA was higher in ApoE ε4 homozygotes than in heterozygotes and noncarriers among patients treated with LEQEMBI. Of the 5 patients treated with LEQEMBI who had symptomatic ARIA (see Incidence of ARIA), 4 were ApoE ε4 homozygotes, 2 of whom experienced severe symptoms. In addition, an increased incidence of symptomatic and overall ARIA in ApoE ε4 homozygotes compared to heterozygotes and noncarriers in patients taking LEQEMBI has been reported in other studies. The recommendations on management of ARIA do not differ between ApoE ε4 carriers and noncarriers [see Dosage and Administration (2.3)]. Consider testing for ApoE ε4 status to inform the risk of developing ARIA when deciding to initiate treatment with LEQEMBI.
Concomitant Antithrombotic Medications

Concomitant Antithrombotic Medication and Other Risk Factors for Intracerebral Hemorrhage

Patients were excluded from enrollment in Study 1 for baseline use of anticoagulant medications. Antiplatelet medications such as aspirin and clopidogrel were allowed. During the study, if anticoagulant medication was used because of intercurrent medical events that required treatment for 4 weeks or less, treatment with LEQEMBI was to be temporarily suspended. Patients who received LEQEMBI and an antithrombotic medication (aspirin, other antiplatelets, or anticoagulants) did not have an increased risk of ARIA-H compared to patients who received placebo and an antithrombotic medication. The majority of exposures to antithrombotic medications were to aspirin; few patients were exposed to other antiplatelet drugs or anticoagulants, limiting any meaningful conclusions about the risk of ARIA or intracerebral hemorrhage in patients taking other antiplatelet drugs or anticoagulants. Because intracerebral hemorrhages greater than 1 cm in diameter have been observed in patients taking LEQEMBI, additional caution should be exercised when considering the administration of antithrombotics or a thrombolytic agent (e.g., tissue plasminogen activator) to a patient already being treated with LEQEMBI.
Cerebral Amyloid Angiopathy

Additionally, patients were excluded from enrollment in Study 1 for the following risk factors for intracerebral hemorrhage: prior cerebral hemorrhage greater than 1 cm in greatest diameter, more than 4 microhemorrhages, superficial siderosis, evidence of vasogenic edema, evidence of cerebral contusion, aneurysm, vascular malformation, infective lesions, multiple lacunar infarcts or stroke involving a major vascular territory, and severe small vessel or white matter disease. Caution should be exercised when considering the use of LEQEMBI in patients with these risk factors.
Questions for the Advisory Committee

• **Discussion:** Discuss the results from Study 301 (CLARITY AD) and whether they provide evidence of clinical benefit of lecanemab for the treatment of Alzheimer’s disease (AD).

• **Vote:** Do the results of Study 301 (CLARITY AD) verify the clinical benefit of lecanemab for the treatment of AD?

• **Discussion:** Discuss the overall benefit/risk assessment of lecanemab for the treatment of AD. Additionally, consider the following subgroups in your assessment:
  – Apolipoprotein E (ApoE) ε4 homozygotes
  – Patients requiring concomitant treatment with anticoagulant agents
  – Patients with cerebral amyloid angiopathy
Backup Slides Shown
Current pharmacovigilance measures for lecanemab

- Expedited reporting of any deaths in ongoing studies and of deaths resulting from cerebral hemorrhage greater than 1 centimeter in size in the postmarketing setting.

- Postmarketing pharmacovigilance to characterize the risk of ARIA and the monitoring for ARIA associated with the use of Leqembi, with biannual reports of ARIA-E and ARIA-H (specifying microhemorrhage or superficial siderosis), along with any incident cerebral hemorrhage greater than 1 centimeter in size.

- Postmarketing pharmacovigilance with biannual reports to identify and analyze cases of vasculitis that occur after use of Leqembi.

- Postmarketing pharmacovigilance to characterize the risk of infusion reactions associated with the use of Leqembi.