Safety and Amyloid Plaque Reduction Effects of Remternetug in Patients with Alzheimer’s Disease: Interim Analysis from a Phase 1 Study

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Eli Lilly and Company, Indianapolis, USA

International Conference on Alzheimer’s and Parkinson’s Diseases (AD/PD)
Gothenburg, Sweden
March 28 – April 1, 2023

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Disclosure

- Yan Jin is an employee and shareholder of Eli Lilly and Company
- J1G-MC-LAKB (NCT04451408) was sponsored by Eli Lilly and Company
- Amyvid® (Florbetapir F 18) was developed at Avid Radiopharmaceuticals and is marketed by Eli Lilly and Company as a radioactive diagnostic agent for Positron Emission Tomography (PET) imaging of the brain to estimate β-amyloid neuritic plaque density; safety and effectiveness of Amyvid has not been established for predicting development of dementia or other neurologic conditions and monitoring responses to therapies
Background

- Remternetug (LY3372993) is an IgG1 monoclonal antibody directed at the pyroglutamate modification of the third amino acid of amyloid-beta peptide that is present only in brain amyloid plaques.

- Preclinical pharmacology studies of remternetug showed dose-dependent amyloid plaque removal in PDAPP mice.

Abbreviations: PDAPP=platelet-derived growth factor–driven human amyloid precursor protein.
Study Overview

- **J1G-MC-LAKB (NCT04451408)** is a phase 1 multi-center, investigator and participant double-blind, randomized multiple ascending dose study.

**Primary Objective:**
Safety and tolerability of remternetug in participants with AD

**Key Secondary Objective:**
Effect of remternetug on brain amyloid plaque level in participants with AD

**Study Population:**
Participants with MCI due to AD or mild to moderate dementia due to AD
- Age: 55-85 inclusive
- Meet florbetapir PET entry criteria based on a central read (≥ 37 CL*)
- MMSE ≥ 16
- MRI: no evidence of ARIA-E, ≤ 4 microhemorrhage, ≤ 1 superficial siderosis, or any evidence of macrohemorrhage

*Patients with amyloid SUVR ≥ 1.17, equivalent to 37 centiloids

Abbreviations: AD=Alzheimer’s disease; ARIA-E= amyloid-related imaging abnormality-edema/effusions; CL=centiloid; MCI=mild cognitive impairment; MAD=multiple ascending dose; MMSE=Mini-Mental State Examination; MRI=magnetic resonance imaging; PET=positron emission tomography; SUVR=standardized uptake ratio value

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**Study Design**

### Screening
- Up to 120 days

### Double-blind treatment period – IV administration
- 169 or 337 days

### Follow-up
- ~85 days

**Participants randomized**
- 5:1 within each cohort

#### Remternetug Regimens
- Remternetug 250 mg or PBO Q4W
- Remternetug 700 mg or PBO Q4W
- Remternetug 1400 mg or PBO Q4W
- Remternetug 2800 mg or PBO Q4W

#### Additional Treatments
- Remternetug or PBO 700 mg Q4W 2 doses
- Remternetug 1400 mg or PBO Q4W (Extension)

### Days
- 0
- 15
- 29
- 85
- 169
- 253
- 337

**Florbetapir PET**
- Days 0, 15, 29, 85, 169

**Immunogenicity**
- Days 0, 15, 29, 85, 169

**MRI**
- Days 0, 15, 29, 85, 169

### Abbreviations
- IV=intravenous; PBO=placebo; PET=positron emission tomography; Q4W=every 4 weeks; MRI=magnetic resonance imaging

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This interim analysis included 41 participants who received at least a single dose of placebo or remternetug:

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Placebo (N=7)</th>
<th>250 mg (N=5)</th>
<th>700 mg (N=10)</th>
<th>1400 mg (N=10)</th>
<th>2800 mg (N=5)</th>
<th>700-1400 mg (N=4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), mean ± SD</td>
<td>79.3 ± 4.03</td>
<td>67.4 ± 7.83</td>
<td>72.6 ± 6.36</td>
<td>74.7 ± 5.03</td>
<td>76.6 ± 6.39</td>
<td>73.0 ± 5.72</td>
</tr>
<tr>
<td>Gender, n (%) women</td>
<td>5 (71.4%)</td>
<td>3 (60.0%)</td>
<td>4 (40.0%)</td>
<td>5 (50.0%)</td>
<td>3 (60.0%)</td>
<td>3 (75.0%)</td>
</tr>
<tr>
<td>Race, n (%) White</td>
<td>7 (100.0%)</td>
<td>5 (100%)</td>
<td>10 (100%)</td>
<td>9 (90.0%)</td>
<td>5 (100%)</td>
<td>4 (100%)</td>
</tr>
<tr>
<td>MMSE, mean ± SD</td>
<td>24.9 ± 4.63</td>
<td>23.0 ± 4.80</td>
<td>25.0 ± 4.14</td>
<td>24.6 ± 4.72</td>
<td>24.0 ± 4.18</td>
<td>23.5 ± 5.45</td>
</tr>
<tr>
<td>APOE ε4 carrier, n (%)</td>
<td>3 (42.9%)</td>
<td>3 (60.0%)</td>
<td>5 (50.0%)</td>
<td>8 (80.0%)</td>
<td>5 (100.0%)</td>
<td>3 (75.0%)</td>
</tr>
<tr>
<td>Amyloid level (CL), mean ± SD</td>
<td>111.27 ± 24.14</td>
<td>92.6 ± 24.70</td>
<td>95.84 ± 42.27</td>
<td>90.78 ± 29.87</td>
<td>82.22 ± 25.59</td>
<td>58.04 ± 14.98</td>
</tr>
</tbody>
</table>

Abbreviations: CL=centiloid; MMSE=Mini-Mental State Examination; N=number of participants; Q4W=once every 4 weeks; SD=standard deviation.
Dose-Dependent Amyloid Plaque Lowering With Remternetuq

Adjusted amyloid mean change from baseline (CL)

<table>
<thead>
<tr>
<th>Days</th>
<th>Placebo</th>
<th>1400 mg Q4W</th>
<th>250 mg Q4W</th>
<th>2800 mg Q4W</th>
<th>700 mg Q4W x 2, 1400 mg Q4W thereafter</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
<td>-20</td>
<td>-40</td>
<td>-60</td>
</tr>
<tr>
<td>85</td>
<td>-100</td>
<td>-80</td>
<td>-60</td>
<td>-40</td>
<td>-20</td>
</tr>
<tr>
<td>169</td>
<td>-120</td>
<td>-100</td>
<td>-80</td>
<td>-60</td>
<td>-40</td>
</tr>
</tbody>
</table>

p<0.001 versus placebo for all except remternetuq 250 mg at day 85 via mixed model repeated measures

References:

Abbreviations: CL=centiloid; PET=positron emission tomography; Q4W=once every 4 weeks

Dotted line = 24.1 CL to indicate the amyloid clearance level

Threshold of 0 CL is an average value in “high certainty” amyloid negative subjects i.e., young (≤45 years) controls

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### Number of participants with safety events or who discontinued early

<table>
<thead>
<tr>
<th>Participants, n (%)</th>
<th>250 mg Remternetug or PBO (N=6)</th>
<th>700 mg Remternetug or PBO (N=12)</th>
<th>1400 mg Remternetug or PBO (N=12)</th>
<th>2800 mg Remternetug or PBO (N=6)</th>
<th>700-1400 mg Remternetug or PBO (N=5)</th>
<th>Total (N=41)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Deaths</strong></td>
<td>0</td>
<td>0</td>
<td>1 (8.3)*</td>
<td>0</td>
<td>0</td>
<td>1 (2.4)</td>
</tr>
<tr>
<td><strong>Serious AE</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ARIA-E, ARIA-H, and suicidal attempt</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (20.0)</td>
<td>1 (2.4)</td>
</tr>
<tr>
<td>COVID-19 pneumonia*</td>
<td>0</td>
<td>0</td>
<td>1 (8.3)</td>
<td>0</td>
<td>0</td>
<td>1 (2.4)</td>
</tr>
<tr>
<td>Pleural effusion*</td>
<td>0</td>
<td>0</td>
<td>1 (8.3)</td>
<td>0</td>
<td>0</td>
<td>1 (2.4)</td>
</tr>
<tr>
<td>Chest pain*</td>
<td>0</td>
<td>1 (8.3)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (2.4)</td>
</tr>
<tr>
<td><strong>Early discontinuation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AEs</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (20.0)</td>
<td>1 (2.4)</td>
</tr>
<tr>
<td>Withdrawal by participant</td>
<td>1 (16.7%)</td>
<td>1 (8.3)</td>
<td>5 (41.7)**</td>
<td>1 (16.7)</td>
<td>0</td>
<td>8 (19.5)</td>
</tr>
</tbody>
</table>

Blinded safety data by dosing cohorts as of May 31, 2022.

*considered not related to study treatment by the investigator (death reported due to COVID-19 pneumonia); ** 4 participants declined to complete the extended treatment duration.

Abbreviations: AE=adverse event; ARIA = amyloid-related imaging; ARIA-E = ARIA-edema/effusion; ARIA-H = ARIA-microhemorrhages and haemosiderin deposits; IV=intravenous; N=number of participants who received at least 1 dose of remternetug or PBO; n=number of participants with at least 1 AE per event type; PBO=placebo
# Treatment-Emergent Adverse Events

## Treatment-emergent adverse events of all causality (≥2 participants)

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>250 mg Remternetug or PBO</th>
<th>700 mg Remternetug or PBO</th>
<th>1400 mg Remternetug or PBO</th>
<th>2800 mg Remternetug or PBO</th>
<th>700-1400 mg Remternetug or PBO</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=6 n (%)</td>
<td>N=12 n (%)</td>
<td>N=12 n (%)</td>
<td>N=6 n (%)</td>
<td>N=5 n (%)</td>
<td>N=41 n (%)</td>
</tr>
<tr>
<td>Participants with ≥1 TEAE, n (%)</td>
<td>0</td>
<td>5 (41.7)</td>
<td>7 (58.3)</td>
<td>4 (66.7)</td>
<td>4 (80.0)</td>
<td>20 (48.8)</td>
</tr>
<tr>
<td>ARIA-E</td>
<td>0</td>
<td>1 (8.3)</td>
<td>3 (25.0)</td>
<td>3 (50.0)</td>
<td>3 (60.0)</td>
<td>10 (24.4)</td>
</tr>
<tr>
<td>ARIA-H</td>
<td>0</td>
<td>1 (8.3)</td>
<td>3 (25.0)</td>
<td>1 (16.7)</td>
<td>2 (40.0)</td>
<td>7 (17.1)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>0</td>
<td>1 (8.3)</td>
<td>0</td>
<td>0</td>
<td>1 (20.0)</td>
<td>2 (4.9)</td>
</tr>
<tr>
<td>Infusion site reaction*</td>
<td>0</td>
<td>1 (8.3)</td>
<td>0</td>
<td>0</td>
<td>1 (20.0)</td>
<td>2 (4.9)</td>
</tr>
</tbody>
</table>

*Infusion site reaction included a case of local reaction at infusion site and a case of infusion site phlebitis.

- No treatment-emergent antidrug antibodies were detected, and no systemic infusion-related reactions occurred following single or multiple administrations of remternetug

Abbreviations: ARIA-E = amyloid-related imaging abnormality-edema/effusion; ARIA-H = amyloid-related imaging abnormality-microhemorrhages and haemosiderin deposits; N = number of participants who received at least 1 dose of remternetug or PBO; n = number of participants with event; PBO = placebo; TEAE = treatment-emergent adverse event.
Incidence of ARIA-E, microhemorrhage, and superficial siderosis based on MRI

<table>
<thead>
<tr>
<th>Participants, n (%)</th>
<th>250 mg Remternetug or PBO (N=6)</th>
<th>700 mg Remternetug or PBO (N=12)</th>
<th>1400 mg Remternetug or PBO (N=12)</th>
<th>2800 mg Remternetug or PBO (N=6)</th>
<th>700-1400 mg Remternetug or PBO (N=5)</th>
<th>Total (N=41)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARIA-E</td>
<td>0</td>
<td>1 (8.3)</td>
<td>3 (25.0)</td>
<td>3 (50.0)</td>
<td>3 (60.0)</td>
<td>10 (24.4)</td>
</tr>
<tr>
<td>Microhemorrhage</td>
<td>0</td>
<td>1 (8.3)</td>
<td>4 (33.3)</td>
<td>2 (33.3)</td>
<td>2 (40.0)</td>
<td>9 (22.0)</td>
</tr>
<tr>
<td>Superficial siderosis</td>
<td>0</td>
<td>0</td>
<td>2 (16.7)</td>
<td>1 (16.7)</td>
<td>1 (20.0)</td>
<td>4 (9.8)</td>
</tr>
</tbody>
</table>

- One participant experienced an SAE of ARIA-E and ARIA-H (microhemorrhage) in the 700-1400 mg titration cohort
  - Symptoms reported: aphasia, imbalance, and visual field defect
  - Symptoms resolved after discontinuation of study drug, and oral steroids
- Remaining participants with ARIA were asymptomatic
- All participants who experienced ARIA were APOE ε4 carriers
- No macrohemorrhages were observed

Abbreviations: APOE=apolipoprotein E; ARIA-E= amyloid-related imaging abnormality-edema/effusions; ARIA-H=amyloid-related imaging abnormality-hemorrhage; N=number of participants with AD who received at least 1 dose of remternetug or PBO; n=number of participants with ARIA; PBO=placebo; SAE=serious adverse event
Conclusions

- Remternetug demonstrated rapid and robust amyloid plaque reduction in participants with AD

- The safety, tolerability, and pharmacokinetic/pharmacodynamic data support the ongoing phase 3 trial (NCT05463731)
Acknowledgements

- We gratefully acknowledge the contribution and dedication of all patients with Alzheimer’s disease, their caregivers, and their families who participated in this study, along with trial site investigators and personnel, and our third-party organization contributors.

- We thank Andrea Abram, Catherine Devadanam, Thomas Harris, and Amanda Potasnik for imaging support and Staci Engle for her assistance with creating this presentation (all employees of Eli Lilly and Company).

- This study was sponsored by Eli Lilly and Company.