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

Mark A. Mintun
Presenter Disclosure Information
Vice-President of Alzheimer's Disease Development, Eli Lilly and Company, Indianapolis, IN, USA
President, Avid Radiopharmaceuticals, Inc. Philadelphia, PA, USA

Eli Lilly and Company, Indianapolis, IN, USA
Background

Accumulation of amyloid-β peptide in the form of amyloid plaques is an early and essential event in the onset of Alzheimer’s disease (AD)

Donanemab is a humanized immunoglobulin G1 antibody specific for an N-terminal pyroglutamate amyloid-β epitope that is present only in mature brain amyloid plaques

Formation of N3 pyroglutamate:

In Phase 1, donanemab significantly reduced amyloid plaque, even with a single dose, in participants with amyloid-positive AD

Q4W = every 4 weeks

Adapted from Selkoe & Hardy EMBO, 2016

Adapted from Jawhar et al., 2011

Lowe et al, CTAD, 2019
**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
- Removes those hypothesized as too advanced to be slowed by anti-amyloid therapy

**TAU PET INCLUSION WINDOW**

- **No/very low tau**
  - Whole brain Tau SUVr < 1.10*
  - EXCLUDED

- **Intermediate tau**

- **High tau**
  - Whole brain Tau SUVr > 1.46
  - EXCLUDED

*SUVR = Standardized Uptake Value ratio. *Visual interpretation also done and took precedent when highly discordant.

EXCLUDED
Study designed to achieve amyloid clearance and then stop dosing

<table>
<thead>
<tr>
<th>Screening</th>
<th>Double-blind treatment period – IV administration</th>
<th>Follow up</th>
</tr>
</thead>
<tbody>
<tr>
<td>One to nine weeks before study treatment start</td>
<td>Safety assessments</td>
<td></td>
</tr>
</tbody>
</table>

- **Donanemab 700mg Q4W 3 doses**:  
  - Week 0: n = 131
  - Week 12: n = 126

- **Donanemab 1400mg Q4W**:  
  - Week 0: n = 1955
  - Week 12: n = 131
  - Week 24: n = 126

- **Donanemab 700mg**:  
  - Week 0: n = 1955
  - Week 12: n = 126

- **Placebo Q4W**:  
  - Week 0: n = 1955
  - Week 12: n = 126

*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

1. 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.
2. One patient was randomized to placebo but discontinued the study before receiving an infusion.

### Notes:
- CL = Centiloids; IV = intravenous; n = number of patients; PET = Positron Emission Tomography; Q4W = every 4 weeks
- Company Confidential © 2021 Eli Lilly and Company
Baseline demographics and key measures balanced across arms

<table>
<thead>
<tr>
<th>Demographic</th>
<th>Placebo (N=126)</th>
<th>Donanemab (N=131)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, % female</td>
<td>51.6%</td>
<td>51.9%</td>
</tr>
<tr>
<td>Age, mean</td>
<td>75.4</td>
<td>75.0</td>
</tr>
<tr>
<td>Race, % Asian</td>
<td></td>
<td></td>
</tr>
<tr>
<td>% Black or AA</td>
<td>1.6%</td>
<td>0.8%</td>
</tr>
<tr>
<td>% White</td>
<td>96.0%</td>
<td>93.1%</td>
</tr>
<tr>
<td>% Other*</td>
<td>0%</td>
<td>2.3%</td>
</tr>
<tr>
<td>Ethnicity, % Hispanic/Latino#</td>
<td>2.4%</td>
<td>3.8%</td>
</tr>
<tr>
<td>Education, % 13 years+</td>
<td>81.0%</td>
<td>74.0%</td>
</tr>
<tr>
<td>APOE 4, % carrier</td>
<td></td>
<td></td>
</tr>
<tr>
<td>% E2/E3</td>
<td>0.8%</td>
<td>0.8%</td>
</tr>
<tr>
<td>% E2/E4</td>
<td>1.6%</td>
<td>1.5%</td>
</tr>
<tr>
<td>% E3/E3</td>
<td>25.0%</td>
<td>26.7%</td>
</tr>
<tr>
<td>% E3/E4</td>
<td>50.0%</td>
<td>51.9%</td>
</tr>
<tr>
<td>% E4/E4</td>
<td>22.6%</td>
<td>19.1%</td>
</tr>
<tr>
<td>AChEI use, %</td>
<td>58.7%</td>
<td>59.5%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Scale/biomarker, mean (SD)</th>
<th>Placebo (N=126)</th>
<th>Donanemab (N=131)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADAS-Cog$_{13}$</td>
<td>27.52 (7.56)</td>
<td>27.63 (7.69)</td>
</tr>
<tr>
<td>ADCS-ADL</td>
<td>66.98 (8.09)</td>
<td>67.35 (8.58)</td>
</tr>
<tr>
<td>ADCS-iADL</td>
<td>48.40 (7.52)</td>
<td>48.86 (7.59)</td>
</tr>
<tr>
<td>iADRS</td>
<td>105.88 (13.22)</td>
<td>106.20 (13.03)</td>
</tr>
<tr>
<td>MMSE</td>
<td>23.69 (2.85)</td>
<td>23.56 (3.06)</td>
</tr>
<tr>
<td>CDR-SB</td>
<td>3.40 (1.74)</td>
<td>3.57 (2.06)</td>
</tr>
<tr>
<td>Amyloid PET Centiloids</td>
<td>101.14 (33.25)</td>
<td>107.61 (35.97)</td>
</tr>
<tr>
<td>Global tau load$\dagger$</td>
<td>0.46 (0.15)</td>
<td>0.47 (0.19)</td>
</tr>
</tbody>
</table>

AA = African American; AChEI = acetylcholinesterase inhibitor; ADAS-Cog$_{13}$ = Alzheimer’s Disease Assessment Scale - Cognitive subscale; ADCS-(i)ADL = Alzheimer’s Disease Cooperative Study- (instrumental) Activities of Daily Living Inventory; APOE 4 = Apolipoprotein E allele 4; CDR-SB = Clinical Dementia Rating Scale Sum of Boxes; iADRS = Integrated Alzheimer’s Disease Rating Scale; MMSE = Mini–Mental State Examination; PET = positron emission tomography; SD = standard deviation

$\dagger$ Includes Multiple & American Indian or Alaska Native.

* Number of participants with non-missing data, used as denominator

$\dagger$ with Tau$^2$
### Safety profile

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

#### Adverse events (AE)

<table>
<thead>
<tr>
<th>Participants, n (%)</th>
<th>Placebo (n=125)</th>
<th>Donanemab (n=131)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<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>

ARIA-E = Amyloid-Related Imaging Abnormalities-Edema/Effusions

*Discontinued treatment due to protocol-defined criteria and patient/principal investigator-cited reasons for discontinuation.

#### Treatment emergent AE ≥5%

<table>
<thead>
<tr>
<th>Preferred Term, n (%)</th>
<th>Placebo (n=125)</th>
<th>Donanemab (n=131)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<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>0.720</td>
</tr>
<tr>
<td>Fall</td>
<td>19 (15.2%)</td>
<td>17 (13.0%)</td>
<td>0.410</td>
</tr>
<tr>
<td>Dizziness</td>
<td>15 (12.0%)</td>
<td>11 (8.4%)</td>
<td>0.294</td>
</tr>
<tr>
<td>Headache</td>
<td>15 (12.0%)</td>
<td>10 (7.6%)</td>
<td></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>

*Discontinued treatment due to protocol-defined criteria and patient/principal investigator-cited reasons for discontinuation.
Outcomes

Primary Outcome: iADRS
Composite measure combining the ADAS-Cog$_{13}$ and the ADCS-iADL, to assess cognition and function, respectively

Secondary Outcomes
- CDR-SB
- ADAS-Cog$_{13}$
- ADCS-iADL
- MMSE

Pathology Biomarkers
- Amyloid deposition
- Tau deposition

iADRS = Integrated Alzheimer's Disease Rating Scale; ADAS-Cog$_{13}$ = Alzheimer’s Disease Assessment Scale-Cognitive subscale; ADCS-iADL = Alzheimer’s Disease Cooperative Study-instrumental Activities of Daily Living Inventory; CDR-SB = Clinical Dementia Rating Scale Sum of Boxes; MMSE = Mini–Mental State Examination
Primary outcome showed treatment with donanemab significantly slowed disease progression by 32% on iADRS at 76 weeks, compared with placebo.

**Graph:**
- **Weeks:** 12, 24, 36, 52, 64, 76
- **Worsening:** Placebo vs. Donanemab
- **LS mean change from baseline (SE):**
  - Placebo: 113, 110, 103, 90, 88, 90, 91
  - Donanemab: 120, 112, 102, 88, 89, 93

- **Statistical Analysis:**
  - MMRM statistical analysis used.
  - iADRS = Integrated Alzheimer's Disease Rating Scale
  - LS = Least Squares
  - MMRM = mixed model for repeated measures
  - n = number of patients
  - SE = Standard Error
  - * p=0.01
  - ** p=0.004
  - * p=0.02
  - * p=0.04

**Legend:**
- Placebo
- Donanemab

**Note:**
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.

MMRM statistical analysis used. iADRS = Integrated Alzheimer's Disease Rating Scale; LS = Least Squares; MMRM = mixed model for repeated measures; n = number of patients; SE = Standard Error; AChEI = acetylcholinesterase inhibitor.

Company Confidential © 2021 Eli Lilly and Company
Observations of ARIA-E did not impact the effect of donanemab in iADRS

AChEI = acetylcholinesterase inhibitor; ARIA-E = Amyloid-Related Imaging Abnormalities-Edema/Effusions; iADRS = Integrated Alzheimer’s Disease Rating Scale; LS = Least Squares; n = number of patients; SE = Standard Error

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.

**ADAS-Cog13**

- **Placebo**: 112, 111, 104, 92, 90, 93
- **Donanemab**: 116, 121, 112, 103, 92, 90, 93

39% slowing

**ADCS-iADL**

- **Placebo**: 114, 112, 111, 102, 91, 92, 93
- **Donanemab**: 111, 110, 102, 90, 91, 92, 93

23% slowing

**MMSE**

- **Placebo**: 115, 112, 108, 100, 89, 87, 91
- **Donanemab**: 118, 107, 101, 90, 89, 87, 91

21% slowing

---

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

Company Confidential © 2021 Eli Lilly and Company
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)

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; MMRM = Mixed-Model Repeated-Measures; MMSE = Mini–Mental State Examination
Secondary outcomes: amyloid lowering

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

Donanemab 'amyloid negative' <24.1 CL, n (%) Donanemab vs. Placebo

<table>
<thead>
<tr>
<th>Weeks</th>
<th>LS Mean Change Δ (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

CI = Confidence Interval; CL = Centiloids; LS = Least Squares; n = number of patients; SE = Standard Error; W = weeks
Amyloid negative defined as < 24.1 CL
Individual examples of amyloid plaque change over 76 weeks

Donanemab

Patient A

Patient B

Placebo

Patient C

= Below 11 Centiloids
Primary measure of TauIQ Global Tau Load showed no significant change. Exploratory Regional Analysis shows SIGNIFICANT DECREASE IN TAU LOAD.

**Global Tau Load (TauIQ)**

- Placebo
- Donanemab

**Regional SUVR with Cerebellar Gray Reference**

- **Frontal Lobe**
- **Occipital Lobe**
- **Parietal Lobe**
- **Mesial Temporal Lobe**
- **Lateral Temporal Lobe**

<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>

Region | Slowing | p-value  
---------|---------|----------|
Frontal Lobe | 59.1% | 0.0020 |
Occipital Lobe | 21.0% | 0.2036 |
Parietal Lobe | 44.6% | 0.0024 |
Mesial Temp. Lobe | NA | 0.0459 |
Lateral Temp. Lobe | 31.8% | 0.0328 |

LS = Least Squares; SD = standard deviation; SE = Standard Error; SUVr=Standardized Uptake Value ratio

# AAL Regions using posterior cerebellum gray matter reference region.
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
In this registration quality Phase 2 study in patients with early symptomatic AD, treatment with donanemab compared with placebo:

- Met the primary endpoint by significantly slowing disease progression on iADRS
- Resulted in positive changes in all clinical secondary outcomes, consistent with the primary outcome
- Rapidly and robustly reduced amyloid plaque deposition
- Slowed regional tau accumulation in exploratory analyses
- Resulted in safety profile similar to Phase 1 findings

AD = Alzheimer’s disease; iADRS = Integrated Alzheimer’s Disease Rating Scale
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).
We gratefully acknowledge the contribution and dedication of all of the patients with AD, their families, and their caregivers who participated in this study, along with trial site investigators and personnel, and members of the data monitoring committee.

We acknowledge contributions from Adam Fleisher, Ann Marie Hake, Cora Sexton, Michael Devous, Anupa Arora, Michael Pontecorvo, and Jennifer Zimmer, current employees of Eli Lilly and Company, as well as Michael Irizarry, a former employee of Eli Lilly and Company.

This study was sponsored by Eli Lilly and Company.
Donanemab Background and Phase 1 results:
- Selkoe DJ & Hardy J, EMBO 2016; doi: 10.15252/emmm.201606210
- Jawhar S et al., J Biol Chem. 2011; doi: 10.1074/jbc.R111.288308
- Fleisher AS et al. Alzheimer's & Dementia 2018; doi: 10.1016/j.jalz.2018.06.2378

Screening based on tau pathology:
TRAILBLAZER-ALZ (NCT03367403), a Phase 2 Disease-Modification Combination Therapy Trial Targeting Multiple Mechanisms of Action Along the Amyloid Pathway

iADRS Endpoint:

Similar incidences of ARIA-E to Phase 1 findings: