NEUROSCIENCE
The presentations for Eli Lilly’s investment community meeting contain forward-looking statements that are based on management’s current expectations, but actual results may differ materially due to various factors. The company’s results may be affected by factors including, but not limited to, the risks and uncertainties in pharmaceutical research and development; competitive developments; regulatory actions; the extent and duration of the effects of the COVID-19 pandemic; litigation and investigations; business development transactions; economic conditions; and changes in laws and regulations, including health care reform.

For additional information about the factors that affect the company’s business, please see the company’s latest Forms 10-K, 10-Q, and any 8-Ks filed with the Securities and Exchange Commission. In addition, certain financial information in this presentation is presented on a non-GAAP basis. Investors should refer to the reconciliations included in these presentations and should consider the company’s non-GAAP measures in addition to, not as a substitute for or superior to, measures prepared in accordance with GAAP.

The company undertakes no duty to update forward-looking statements except as required by applicable law.
MARK MINTUN, M.D.
President of Neuroscience Research and Development, and President of Avid Radiopharmaceuticals
NEURODEGENERATION UNMET NEED
THE URGENT PROBLEM OF ALZHEIMER’S AND OTHER DEMENTIA

**NEW CASES:** Someone in the United States develops Alzheimer’s disease (AD) every 65 seconds. Alzheimer’s disease is the sixth-leading cause of death in the United States.

**HEALTH:** Today, 5.8 million Americans are living with Alzheimer’s disease, including an estimated 200,000 under the age of 65. By 2050, up to 14 million may have the disease.

**ECONOMICS:** In 2019, 16 million Americans provided 18.5 billion hours of unpaid care for a person living with Alzheimer’s disease or other dementia – an economic value of $234 billion.

**Non-AD Dementias:**
There are no current disease modifying treatments for PD, HD, FTD, ALS and other diseases impacting millions of patients. These diseases have similar types of protein misfolding and could respond to the same approaches being developed against AD.

---

2019 Alzheimer’s Disease Facts and Figures – Alzheimer’s Association; PD = Parkinson’s Disease; HD = Huntington’s Disease; FTD = Frontotemporal Dementia; ALS = Amyotrophic lateral sclerosis

Not for promotional use

2021 INVESTMENT COMMUNITY MEETING
NEURODEGENERATION FOCUS AND STRATEGY

Create diagnostics to enable effective treatment

Intervene earlier

Multiple therapies to attack disease pathologies

New platforms for genetic medicine delivery

First radioactive diagnostic agent approved by the FDA for PET imaging of the brain to estimate beta-amyloid neuritic plaque density

Only approved diagnostic to image tau neurofibrillary tangles in the brain

Plasma Phospho-tau217
Blood-based assay being developed as potential Early Diagnostic Biomarker of Alzheimer’s Disease
NEURODEGENERATION FOCUS AND STRATEGY

Create diagnostics to enable effective treatment

Intervene earlier

Multiple therapies to attack disease pathologies

New platforms for genetic medicine delivery

Can we turn back the clock on amyloid accumulation BEFORE brain damage and symptoms?

Adapted from Selkoe & Hardy EMBO, 2016

AD = Alzheimer's disease; CSF = Cerebrospinal Fluid; MCI = Mild Cognitive Impairment

Not for promotional use
NEURODEGENERATION FOCUS AND STRATEGY

Create diagnostics to enable effective treatment

Intervene earlier

Multiple therapies to attack disease pathologies

New platforms for genetic medicine delivery

Next frontier to target tau pathology beyond anti-amyloid therapy
NEURODEGENERATION FOCUS AND STRATEGY

Create diagnostics to enable effective treatment

Intervene earlier

Multiple therapies to attack disease pathologies

New platforms for genetic medicine delivery

Focus on monogenic diseases and broaden into polygenic diseases

Not for promotional use
Donanemab is an immunoglobulin G1 antibody specific for an N-terminal pyroglutamate amyloid-β epitope that is present only in mature brain amyloid plaques.

Phase 2 primary outcome showed donanemab significantly slowed clinical progression by 32% on iADRS at 76 weeks, compared with placebo.

Taking on the Challenges Ahead

**Advance the Science**
Advance scientific understanding of plaque lowering and of ARIA

**Find and Treat Pathology; Develop AD Ecosystem**
Advance accurate AD diagnosis; Establish diagnostic & infusion infrastructure

**Demonstrate the Value of Anti-Amyloid Therapy**
Confirmatory trial; National Coverage Analysis (NCA) Leadership; Pilot innovative models
### SAFETY & TOLERABILITY

<table>
<thead>
<tr>
<th>Overview of Adverse Events, 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>0.62</td>
</tr>
<tr>
<td>SAEs</td>
<td>22 (17.6)</td>
<td>23 (17.6)</td>
<td>&gt;1.00</td>
</tr>
<tr>
<td>Treatment discontinuations due to AE*</td>
<td>9 (7.2)</td>
<td>40 (30.3)</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>TEAEs</td>
<td>113 (90.4)</td>
<td>119 (90.8)</td>
<td>&gt;1.00</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment Emergent Adverse Events &gt;5% Incidence, n (%)</th>
<th></th>
<th></th>
<th></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>Fall</td>
<td>19 (15.2)</td>
<td>17 (13.0)</td>
<td>0.72</td>
</tr>
<tr>
<td>Dizziness</td>
<td>15 (12.0)</td>
<td>11 (8.4)</td>
<td>0.41</td>
</tr>
<tr>
<td>Headache</td>
<td>15 (12.0)</td>
<td>10 (7.6)</td>
<td>0.29</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;1.00</td>
</tr>
<tr>
<td>Nausea</td>
<td>4 (3.2)</td>
<td>14 (10.7)</td>
<td>0.03</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>9 (7.2)</td>
<td>9 (6.9)</td>
<td>&gt;1.00</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>5 (4.0)</td>
<td>13 (9.9)</td>
<td>0.09</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>5 (4.0)</td>
<td>11 (8.4)</td>
<td>0.20</td>
</tr>
<tr>
<td>ARIA-H</td>
<td>4 (3.2)</td>
<td>11 (8.4)</td>
<td>0.11</td>
</tr>
<tr>
<td>Cerebral microhemorrhage</td>
<td>3 (2.4)</td>
<td>10 (7.6)</td>
<td>0.09</td>
</tr>
<tr>
<td>Infusion-Related Reaction</td>
<td>0 (0.0)</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>0.77</td>
</tr>
<tr>
<td>Depression</td>
<td>8 (6.4)</td>
<td>6 (4.6)</td>
<td>0.59</td>
</tr>
<tr>
<td>Contusion</td>
<td>10 (8.0)</td>
<td>9 (6.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Vomiting</td>
<td>3 (2.4)</td>
<td>7 (5.3)</td>
<td>0.34</td>
</tr>
<tr>
<td>Anxiety</td>
<td>2 (1.6)</td>
<td>7 (5.3)</td>
<td>0.17</td>
</tr>
</tbody>
</table>

SAE = Serious Adverse Event; TEAE = Treatment-Emergent Adverse Event; ARIA-E = Amyloid-Related Imaging Abnormalities with Edema/Effusions; ARIA-H = Amyloid-Related Imaging Abnormalities with hemosiderin deposits

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

Not for promotional use

### FINDINGS

- Safety profile in line with Phase 1 results; no new safety signals observed
- Rate of symptomatic ARIA-E was 6% in the treatment arm (with 27% showing any ARIA-E), similar to other plaque-clearing agents
- Treatment discontinuation due to ARIA was driven by strict protocol criteria
- We remain confident in the risk/benefit profile of donanemab, though note an outstanding issue for the field is the development of strategies for avoidance and management of ARIA
- We look forward to contributing to solutions for managing symptomatic ARIA risk and continue to work closely with stakeholders in the Alzheimer’s field
**DONANEMAB**

**BOTH AMYLOID PLAQUE AND PLASMA P-TAU217 WERE SIGNIFICANTLY LOWERED WITH DONANEMAB**

---

**Amyloid plaque significantly lowered with donanemab treatment¹**

![Graph showing the adjusted mean change in amyloid PET (Centiloids) over weeks.](image)

- Placebo
- Donanemab

---

**Plasma P-tau217 significantly lowered with donanemab treatment²**

![Graph showing the LS mean change of log₁₀ plasma P-tau217 over weeks.](image)

- Placebo
- Donanemab

---

**Key Findings**

- Previously showed evidence for slowing regional tau tangles by PET
- Now with additional evidence that donanemab reduced the tau pathological cascade

---

* p<0.05; ** p<0.01; *** p<0.001 vs placebo; ¹secondary endpoint; ²exploratory objective

TRAILBLAZER-ALZ Mixed Model Repeated Measures (MMRM) analysis; Data points show mean +/- standard error; LS = Least Square; PET = Positron Emission Tomography; p = p-value

Not for promotional use

---

2021 INVESTMENT COMMUNITY MEETING
DONANEMAB
BOTH AMYLOID PLAQUE AND PLASMA P-TAU217 REDUCTION CONTINUED FOR ONE YEAR AFTER DOSING STOPPED

Amyloid plaque significantly lowered with donanemab treatment¹

Plasma P-tau217 significantly lowered with donanemab treatment²

Adjusted mean change in amyloid PET (Centiloids)

Placebo
Donanemab – stopped at 24 weeks due to complete amyloid clearance

LS mean change of log10 plasma P-tau217

Placebo
Donanemab – stopped at 24 weeks due to complete amyloid clearance

Drop in P-tau217 was still present one year after clearing plaques and stopping donanemab treatment

---

* p<0.05; ** p<0.01; *** p<0.001 vs placebo; ¹exploratory objective; ²exploratory objective
TRAILBLAZER-ALZ Mixed Model Repeated Measures (MMRM) analysis; Data points show mean +/- standard error; LS = Least Square; p = p-value

Not for promotional use
Elevated GFAP is a highly specific inflammatory biomarker of astrogliosis in the brain.

Donanemab lowered plasma GFAP similar to the reductions seen in amyloid and P-tau.

Strengthens the evidence that donanemab treatment is associated with reducing multiple pathological processes of Alzheimer's disease.

**REDUCED INFLAMMATORY MARKER**

Gliarial Fibrillary Acidic Protein (GFAP) significantly lowered with donanemab treatment\(^1\)

*\(^{p<0.05}; \; **\(^{p<0.01}; \; ***\(^{p<0.001}\) vs placebo; \(^1^\)exploratory objective

TRAILBLAZER-ALZ Mixed Model Repeated Measures (MMRM) analysis; Data points show mean +/- standard error; LS = Least Square; p = p-value

*Not for promotional use*
P-TAU 217 PLASMA ASSAY MAY TRANSFORM AD DIAGNOSIS
P-TAU217 PREDICTED AD PATHOLOGY IN A RESEARCH SETTING

P-tau217 also predicted amyloid-PET with an AUC of 0.87

Data from Palmqvist et al, JAMA 2020; AD = Alzheimer’s disease; PET = Positron Emission Tomography; p = p-value; AUC = Area Under the Curve; NFL = Neurofilament Light Chain

Not for promotional use
P-TAU 217 PLASMA ASSAY MAY TRANSFORM AD DIAGNOSIS
LEVERAGING PLASMA P-TAU217 FOR FUTURE CLINICAL CARE

Potential to speed up diagnosis, decrease biomarker testing cost and provide more convenient access to patients

- Represents evolution towards less invasive diagnostics for patients
- Accessibility should lower the barrier for AD biomarker testing
- Investigating how to best transition our research experience into clinical practice
- Will look to combine Lilly’s expertise with established diagnostic partners
TRAILBLAZER ALZ-3
PREVENTION STUDY IN COGNITIVELY UNIMPAIRED

TRIAL DESIGN

- Preclinical AD event-driven prevention study
  - 3300 participant randomized trial measuring the Global Scale for Clinical Dementia Rating as primary endpoint
  - Target individuals 55-80 years of age who are cognitively unimpaired but with evidence of AD disease pathology

- P-tau217 assay used as part of inclusion criteria
  - New paradigm for clinical trial recruitment
  - Increased flexibility for screening activities, e.g., mobile units

- Decentralized trial with central services
  - Decentralized sites, including those in under-represented communities, to enable recruitment of diverse populations
  - Central safety monitoring including MRIs for detecting ARIA

- Informed by learnings from solanezumab A4 study

GOALS

- To assess whether a short course of donanemab treatment (9 infusions) at the start of the trial can slow or prevent progression to the clinical stages of AD
- Plan to complete enrollment by the end of 2022
- Anticipate 3-4 years after last patient enrolled for events to accrue for primary endpoint

AD = Alzheimer’s disease
Not for promotional use

2021 INVESTMENT COMMUNITY MEETING
TRAILBLAZER ALZ-4
HEAD-TO-HEAD PHASE 3 STUDY COMPARING DONANEMAB TO ADUCANUMAB

TRIAL DESIGN & TIMELINE

- 200 patient, 18-month treatment study measuring change in amyloid at three time points (6, 12 & 18 months)
- Enrollment to be completed 1Q 2022
- Primary readout at 6-month time point; expected in the second half of 2022

GOALS & RATIONALE

- To assess superiority of brain amyloid plaque clearance in early symptomatic population
- First trial to provide direct comparison between amyloid-lowering agents for biomarker efficacy
- Given plaque lowering is FDA-approved surrogate biomarker for efficacy, the magnitude and speed of plaque lowering should be critical basis of comparison
N3PG4 (LY3372993)
ONGOING PHASE 1B SHOWS DEEP PLAQUE CLEARANCE AND SAFETY PROFILE CONSISTENT WITH AMYLOID-LOWERING CLASS

Phase 1 Data

Amyloid PET Scans for a Patient

Aiming for next generation N3pG amyloid lowering agent with flexible dosing regimens, including subcutaneous, to address the different needs of the Alzheimer’s disease population.

Prioritizing safety and more-convenient patient experience.

Based on Phase 1 results, potential start of pivotal studies are expected in 2022.

Note: Figures in parenthesis indicate standard deviation; CL level of zero indicates average amyloid level of a cognitively normal young control subject.
TARGETING TAU FOR ALZHEIMER’S DISEASE

Addressing various phases of tau pathology

Suppress Tau expression using multiple approaches
Block Tau aggregation with small molecule approaches, such as OGA inhibitor
Stop Transneuronal Tau pathology spreading

Note: zagotenemab development was discontinued
Not for promotional use

2021 INVESTMENT COMMUNITY MEETING
O-GlcNAcase (OGA) INHIBITOR (LY3372689)
AN ORAL ANTI-TAU SMALL MOLECULE WITH THE POTENTIAL TO MODIFY ALZHEIMER’S DISEASE

PRE-CLINICAL DATA

- Hit the target
  - Demonstrated >80% enzyme occupancy (EO)
- Reduced AD pathology
  - 50% reduction of tau pathology
- Slowed neurodegeneration
  - 40% reduction of brain atrophy
- Improved memory decline in mouse models

PHASE 1 DATA

- No dose limiting Adverse Events
- >80% EO achieved at 1mg dose
- Robust EO and manageable safety profile confidently inform Phase 2 dosing

PHASE 2 DESIGN

- Target population
  - Early symptomatic Alzheimer’s disease
  - Evidence of tau pathology by PET scan
- Trial Design
  - Three arms (placebo, high dose, low dose)
  - Randomized, 110 patients/arm
  - Estimated enrollment completion: 2H 2022
- Primary endpoint
  - Integrated Alzheimer’s Disease Rating Scale (IADRS) at 76-124 weeks with common close design in those with intermediate levels of brain tau
- Independent Data Safety Monitoring reviews

AD = Alzheimer’s disease
Not for promotional use

2021 INVESTMENT COMMUNITY MEETING
ANTI-TAU siRNA DEVELOPMENT

Tau therapeutic hypothesis...

Pathogenesis of tauopathies (including AD/PSP)

- MAPT (tau) transcription
  - MAPT mRNA expression
  - Tau protein expression
    - Tau aggregation (NFTs) and propagation (spread)
    - Neurodegeneration
  - Clinical symptoms and progression

siRNA to degrade mRNA

Reducing tau protein expression will prevent downstream effects

MAPT (Tau) mRNA Reduction...

MAPT mRNA Reduction in NHP Cortical Neurons following CSF Injection: MAPT SiRNA

- Presence of MAPT mRNA – white staining
- DAPI (nuclei)
- NeuN (neuronal marker)
PREVAIL THERAPEUTICS: FOCUS ON GENE THERAPY
THREE ON-GOING PHASE 1/2 CLINICAL TRIALS (OPEN-LABEL, DOSE-ESCALATING)

REPLACE GBA1 ENZYME

PD-GBA Patients
PR001

- Moderate to severe Parkinson’s disease
- Single or biallelic GBA1 mutations
- Anticipated LPE: Mid-2022

Type 2 Gaucher Patients
PR001

- Neurological signs & symptoms consistent with Type 2 Gaucher disease
- Biallelic GBA1 mutations
- Anticipated LPE: 2023

FTD-GRN Patients
PR006

- Single pathogenic GRN mutation
- 30-80 years old
- Symptomatic disease stage
- Anticipated LPE: 2023

PD-GBA = Parkinson’s disease glucosylceramidase beta; FTD GRN = Frontotemporal dementia progranulin; LPE = Last Patient Enrolled
Not for promotional use

2021 INVESTMENT COMMUNITY MEETING
PREVAIL THERAPEUTICS: PRELIMINARY BIOMARKER DATA
KEY CSF BIOMARKER GOAL ACHIEVED ACROSS ALL THREE TRIALS

PD-GBA (GD1) patient treated with PR001

CSF GCase Activity (μmol/L/d)

<table>
<thead>
<tr>
<th></th>
<th>BL</th>
<th>Mo 3</th>
<th>Mo 9</th>
</tr>
</thead>
<tbody>
<tr>
<td>CSF GCase Activity</td>
<td>&lt;LOQ</td>
<td>3.0</td>
<td>2.9</td>
</tr>
</tbody>
</table>

GD2 patient treated with PR001

CSF GCase Activity (μmol/L/d)

<table>
<thead>
<tr>
<th></th>
<th>BL</th>
<th>Mo 1</th>
<th>Mo 4</th>
<th>Mo 6</th>
<th>Mo 7</th>
</tr>
</thead>
<tbody>
<tr>
<td>CSF GCase Activity</td>
<td>0.8</td>
<td>1.0</td>
<td>4.7</td>
<td>4.3</td>
<td>4.9</td>
</tr>
</tbody>
</table>

FTD-GRN patient treated with PR006

CSF PRGN Protein (ng/mL)

<table>
<thead>
<tr>
<th></th>
<th>BL</th>
<th>Mo 2</th>
<th>Mo 3</th>
<th>Mo 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>CSF PRGN Protein</td>
<td>2.6</td>
<td>7.1</td>
<td>5.5</td>
<td>5.6</td>
</tr>
</tbody>
</table>

Cut off = 3.4 ng/mL

CSF = Cerebrospinal fluid; GBA1 = mutation associated with Parkinson’s disease subtype; T2 = type 2; GRN = mutation associated with frontotemporal dementia subtype; LOQ = Limit of Quantification; BL = Baseline; Mo = Month; GCase = Glucocerebrosidase; PRGN = Progranulin

Not for promotional use
CHRONIC PAIN IS A PUBLIC HEALTH CRISIS

1.7B
1 in 5 people suffer from chronic pain globally \(^1\)

#1
Most common cause of long-term disability\(^2,3\)

78%
Of chronic pain patients are unsatisfied with treatment\(^4\)

> $1T
Annual cost of chronic pain\(^5,6\) – more than cancer, heart disease and diabetes combined\(^7\)

\(^1\) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3201936/
\(^2\) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6676152/
\(^5\) Combined estimates from US, EU, JP
\(^6\) https://www.ncbi.nlm.nih.gov/books/NBK92523/

Not for promotional use

2021 INVESTMENT COMMUNITY MEETING
WHERE WE WERE...

PAIN PIPELINE (DECEMBER 2018)

Gap existed between late phase and discovery pipeline
DEVELOPING INNOVATIVE SOLUTIONS FOR PAIN

STRATEGIC APPROACH

Challenges for Pain Research
- Animal models do not identify responsive populations
- Many credible targets but few with POC in patients

Rapid Clinical POCs
- Lilly launched the first Pain Master Protocol (PMP)
- Three assets entered PMP to date.
- Expected to have 13 new POC readouts by 2023-end (including 12 from PMP)

Building Neuronal Health Platform
- IND-ready programs for neuronal degeneration
- Evaluating targets to repair damage

Business Development
- Four Pain deals in 3 years (SSTR4 agonist, TRPA1 antagonist, P2X7 inhibitor, and SARM1 inhibitor)

PAIN PIPELINE (DECEMBER 2021)

Lilly has significantly grown early pipeline (seven molecules between CS and Ph2 today)

POC = Proof of Concept; IND = Investigational New Drug
Not for promotional use

2021 INVESTMENT COMMUNITY MEETING
Note: select pre-clinical assets listed, most of which were discussed at the Lilly Investment Community meeting on December 15, 2021; NME = new molecular entity; NILEX = new indication or line extension
Not for promotional use
Lilly is an established leader with a deep commitment to advance AD research

- Our work on amyloid imaging transformed the field and enabled the current generation of plaque-clearing antibodies
- Our work on tau imaging raised the bar on staging AD pathology and supported our successful results in TRAILBLAZER-ALZ
- Our ongoing work on plasma biomarkers, particularly pTau217, may enable new advances in diagnosis and disease monitoring for next generation of drug development

Donanemab is well positioned to be a differentiated solution for patients, if approved

- Deep and rapid amyloid removal associated with statistically significant slowing in primary endpoint
- Multiple pathology-related biomarkers support limited dosing regimen

Lilly is rapidly moving beyond anti-amyloid medicines for AD with novel targets using next generation platform modalities, both for neurodegeneration and pain