Lilly releases donanemab data that demonstrated relationship between reduction of amyloid plaque and slowing of cognitive decline

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- P-tau217 in blood showed promise as additional biomarker of efficacy
- Donanemab treatment led to 24% lowering of P-tau217 from baseline

INDIANAPOLIS, July 29, 2021 /PRNewswire/ -- Today at the Alzheimer's Association International Conference© (AAIC© 2021), Eli Lilly and Company (NYSE: LLY) presented two new exploratory analyses of data from the Phase 2 TRAILBLAZER-ALZ study. In the first, greater amyloid plaque changes following donanemab treatment was highly associated with less cognitive decline and participants with greater plaque clearance at 24 weeks of treatment showed less tau progression. In the second, Lilly shared data showing that treatment with donanemab drives a rapid reduction of a biomarker reflecting Alzheimer's disease pathology, plasma P-tau217, which was detected within 12 weeks.

Donanemab is an investigational antibody that targets a modified form of beta amyloid plaque called N3pG. In June 2021, Lilly announced the U.S. Food and Drug Administration (FDA) had granted Breakthrough Therapy designation for donanemab based on the Phase 2 data. No additional safety analyses were performed related to the presentations; for information on donanemab's safety profile, reference the previous publication.

"We are excited by these promising results, which provide further evidence on the potential for donanemab to slow disease progression for people with early symptomatic Alzheimer's disease," said Mark Mintun, M.D., vice president of pain and neurodegeneration, Lilly. "Importantly, these data link the mechanism of action of donanemab, plaque clearance, with positive effects on both clinical outcomes and brain tau pathology."

In the first oral presentation, donanemab induced rapid amyloid plaque reduction at 24 weeks in participants with early symptomatic AD, with the most rapid clearance in subjects with the most severe plaque burden at baseline. The subset of participants who reached complete amyloid plaque clearance at 24 weeks (defined as an amyloid level of <24.1CL) were able to stop or reduce dosing of donanemab earlier than other patients. Among those who achieved complete amyloid plaque clearance at 24 weeks and had a blinded switch to placebo, an exposure-response model showed minimal amyloid re-accumulation over the next year.

Additionally, among those who reached early complete amyloid plaque clearance status at 24 weeks, a flortaucipir positron emission tomography (PET) scan at 76 weeks showed a significant decrease of tau spread – a predictive biomarker for AD progression – over 76 weeks in frontal, parietal and temporal brain regions compared to placebo.

Greater amyloid plaque change at 24 weeks was also associated with improved Integrated Alzheimer's Disease Rating Scale (iADRS) score, a validated, composite measure that combines two well-established instruments used to assess cognition and daily function in AD clinical trials. Additionally, pharmacokinetic/pharmacodynamic modeling showed that greater relative amyloid plaque clearance was correlated with greater clinical benefit.

A second oral presentation focused on plasma P-tau217 (tau phosphorylated at threonine 217), a research blood-biomarker developed by Lilly, associated with amyloid and tau pathology and diagnosis of Alzheimer's disease. Planned analyses showed that treatment with donanemab resulted in early reduction of P-tau217 (LS mean log10 change -0.04) and showed significant reduction ($p<0.01$) by the 3-month timepoint compared to placebo (LS mean log10 change 0). Decreased P-tau217 correlated significantly with amyloid change at all timepoints, at 24 weeks ($R = 0.394$, $p<0.0001$) and 76 weeks ($R = 0.492$, $p<0.0001$).

"Notably, these data support the amyloid cascade hypothesis and suggest that amyloid-related tauopathy can be altered with donanemab's impact on plaque clearance. Furthermore, the data support that early and profound amyloid clearance may translate into clinical benefit for patients," said John Sims, senior medical director of neurodegeneration and co-author of the analysis.

About Donanemab
Donanemab is an investigational antibody that targets a modified form of beta amyloid plaque called N3pG. Results from a Phase 2 study of

donanemab were announced and published earlier this year, and in June Lilly announced the U.S. Food and Drug Administration (FDA) had granted Breakthrough Therapy designation for donanemab based on the Phase 2 data. Lilly plans to submit a biologics license application (BLA) for donanemab under the accelerated approval pathway later this year.

About TRAILBLAZER-ALZ
In the TRAILBLAZER-ALZ study, donanemab dosing was 700 mg every four weeks for the first three doses, then 1400mg every four weeks, for up to 76 weeks. Planned blinded dose reduction evaluations occurred at 24 and 52 weeks.

Donanemab is also being studied in the ongoing Phase 3 TRAILBLAZER-ALZ 2 study in early, symptomatic Alzheimer's disease patients. TRAILBLAZER-ALZ 3, a prevention study, will evaluate whether treatment with donanemab can prevent the clinical progression of Alzheimer's disease in trial participants before clinical impairment begins. Visit LillyMemoryTrials.com for additional information on enrolling in Alzheimer's disease trials.

About Alzheimer's Disease
Alzheimer's disease is a fatal illness that causes progressive decline in memory and other aspects of cognition. Dementia due to Alzheimer's disease is the most common form of dementia, accounting for 60 to 80 percent of all cases.[1] There are currently over 50 million people living with dementia around the world, with numbers expected to increase to nearly 152 million by 2050.[2] Almost 10 million new cases of dementia are diagnosed each year worldwide, implying one new case every 3 seconds, and a significant increase in the caregiving burden placed on society and families. In the US alone, there was an increase of 8 million new caregivers from 2015 to 2020.[3] The current annual societal and economic cost of dementia is estimated at $1 trillion, an amount that is expected to double by 2030 unless we find a way to slow the disease.[2]

In an addition to age and family history of AD, the greatest risk factor for developing AD is the presence of the apolipoprotein E ε4 (APOE4) allele.[1] Having one APOE4 allele increases the risk of developing Alzheimer's disease by approximately three times compared with those with two copies of the APOE3 form. Those who inherit two copies of the APOE4 allele have an 8 - 12-fold risk. In addition, those with the APOE4 allele are more likely to have beta-amyloid accumulation and Alzheimer's dementia at a younger age than those with the APOE2 or APOE3 forms of the APOE gene.

About Eli Lilly and Company
Lilly is a global healthcare leader that unites caring with discovery to make life better for people around the world. We were founded more than a century ago by a man committed to creating high-quality medicines that meet real needs, and today we remain true to that mission in all our work. Across the globe, Lilly employees work to discover and bring life-changing medicines to those who need them, improve the understanding and management of disease, and give back to communities through philanthropy and volunteerism. To learn more about Lilly, please visit us at lilly.com and lilly.com/newsroom. P-LLY

Lilly Cautionary Statement Regarding Forward-Looking Statements
This press release contains forward-looking statements (as that term is defined in the Private Securities Litigation Reform Act of 1995) about donanemab as a potential treatment for people with Alzheimer's disease and reflects Lilly's current beliefs and expectations. However, as with any such undertaking, there are substantial risks and uncertainties in the process of drug research, development, and commercialization. Among other things, there is no guarantee that future study results will be consistent with study results to date, that donanemab will prove to be a safe and effective treatment for Alzheimer's disease, that donanemab will receive regulatory approval, that Lilly will realize the expected benefits of the collaboration, or that Lilly will execute its strategy as expected. For further discussion of these and other risks and uncertainties, see Lilly's Form 10-K and Form 10-Q filings with the United States Securities and Exchange Commission. Except as required by law, Lilly undertakes no duty to update forward-looking statements to reflect events after the date of this release.

1. Alzheimer's Association. Facts and Figures. https://www.alz.org/alzheimers-dementia/facts-figures. Accessed December 8, 2020.
2. Alzheimer's Disease International. World Alzheimer Report 2019. https://www.alz.co.uk/research/WorldAlzheimerReport2019.pdf. Accessed December 8, 2020.
3. AARP. 2020 Report: Caregiving in the U.S. https://www.aarp.org/content/dam/aarp/ppi/2020/05/full-report-caregiving-in-the-united-states.doi.10.26419-2Fppi.00103.001.pdf. Accessed December 8, 2020.

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