Lilly's donanemab slowed Alzheimer's disease progression in Phase 2 trial: full data presented at AD/PD™ 2021 and published in NEJM

March 13, 2021

Findings from the primary endpoint supported by consistency of all secondary outcome measures assessing cognition and function

TRAILBLAZER-ALZ is the first study to screen and enroll patients based on their tau pathology

Biomarker results suggest potential for long-term disease modification following fixed duration treatment with slowing of tau accumulation across key brain regions

INDIANAPOLIS, March 13, 2021 /PRNewswire/ -- Phase 2 TRAILBLAZER-ALZ results presented today by Eli Lilly and Company (NYSE: LLY) at the 15th International Conference on Alzheimer's & Parkinson Diseases™ 2021 (AD/PD™ 2021) held virtually March 9-14, 2021 and published simultaneously in the *New England Journal of Medicine* (NEJM) expand on previously reported top-line data that found donanemab met its primary endpoint and showed significant slowing of decline on the integrated Alzheimer's Disease Rating Scale (iADRS), a composite measure of cognition and daily function, in patients with early symptomatic Alzheimer's disease compared to placebo[1,2].

Additionally, data from secondary analyses showed donanemab consistently slowed cognitive and functional decline, with ranges between 20-40 percent in all secondary endpoints [Clinical Dementia Rating Scale Sum of Boxes (CDR-SB), Alzheimer's Disease Assessment Scale-Cognitive (ADAS-Cog13), Alzheimer's Disease Cooperative Study-instrumental Activities of Daily Living (ADCS-iADL), Mini-Mental State Examination (MMSE)] with nominal statistical significance at multiple times compared to placebo. Further, prespecified exploratory analyses showed donanemab slowed the accumulation of tau across key brain regions in patients affected by Alzheimer's disease.

"We are confident in the results of the TRAILBLAZER-ALZ study," said Daniel Skovronsky, M.D., Ph.D., Lilly's chief scientific officer and president of Lilly Research Laboratories. "This is the first late-stage study in Alzheimer's disease to meet its primary endpoint at the primary analysis. Donanemab has the potential to become a very important treatment for Alzheimer's disease. We were pleased to see not only slowing of cognitive and functional decline, but also very substantial clearance of amyloid plaques and slowing of spread of tau pathology. The constellation of clinical and biomarker results indicates the potential for long-term disease modification. We are grateful to the patients, caregivers, and investigators who participated in this landmark study."

Specifically, at 76 weeks compared to baseline, treatment with donanemab slowed decline by 32 percent compared to placebo as measured by the iADRS, which was statistically significant. As early as nine months (36 weeks) after initiation of treatment, a significant difference in decline by iADRS was observed.

In addition, 40 percent of participants treated with donanemab achieved amyloid negativity as early as six months after starting treatment and 68 percent achieved this target by 18 months. Donanemab is a monoclonal antibody that was designed to bind a specific form of post-translationally modified Aß, N-terminal pyroglutamate, and thereby yield rapid and complete clearance of amyloid plaques.

"Tau has become increasingly validated as a predictive biomarker for Alzheimer's disease progression, as shown again in this trial," said Liana G. Apostolova, M.D., M.Sc., FAAN, Indiana University (IU) Distinguished Professor and Barbara and Peer Baekgaard Professor in Alzheimer's Disease Research at IU School of Medicine. "A key insight of the results from the TRAILBLAZER-ALZ study is that donanemab not only significantly reduced the amount of amyloid deposition in these patients but also slowed the clinical progression of the disease suggesting that this could be a disease-modifying therapy. We believe these amyloid and tau imaging data lay the foundation for precision medicine-based Alzheimer's disease treatments."

The safety profile of donanemab was consistent with observations from Phase 1 data. In the donanemab treatment group, amyloid-related imaging abnormalities – edema (ARIA-E) occurred in 26.7 percent of treated participants, with an overall incidence of 6.1 percent experiencing symptomatic ARIA-E; the majority ARIA-E cases occurred within the first 12 weeks after initiation of treatment. Other common AEs in the donanemab treatment group include ARIA-H related events like microhemorrhages (7.6 percent) and superficial siderosis of central nervous system (13.7 percent), nausea (10.7 percent), and infusion-related reaction (IRR) (7.6 percent). Serious IRR or hypersensitivity occurred in 2.3 percent of participants treated with donanemab. In the donanemab arm, 30.5 percent of patients discontinued treatment due to an adverse event and half of these discontinuations were due to ARIA-related events. Patients with treatment discontinuations were allowed to continue in the trial.

"As a clinician and researcher, I'm particularly encouraged by the significant plaque lowering and the slowing of clinical decline with donanemab," said Stephen P. Salloway, M.S., M.D., Director of the Memory and Aging Program and the Department of Neurology at Butler Hospital and Martin M. Zucker professor of Psychiatry and Human Behavior, Department of Neurology, Warren Alpert Medical School of Brown University. "The donanemab results are a significant and encouraging milestone for people impacted by Alzheimer's disease and we are eager to continue on in this fight."

Discussions with regulators are ongoing and an update on the TRAILBLAZER clinical trial program will be provided on a webcast on Monday, March 15 at 10:30 AM EDT including an update on the ongoing TRAILBLAZER-ALZ 2 trial. To learn more about the TRAILBLAZER-ALZ 2 study or to see if you prequalify, visit www.trailblazer2study.com.

About TRAILBLAZER-ALZ Study

TRAILBLAZER-ALZ (NCT03367403) is a randomized, placebo-controlled, double-blind, multi-center Phase 2 study to assess the safety, tolerability and efficacy of donanemab in patients with early symptomatic Alzheimer's disease. The trial enrolled 272 patients who were selected based on cognitive assessments in conjunction with amyloid plaque imaging and tau staging by PET imaging. The study's primary endpoint is change from baseline until 76 weeks in the Integrated Alzheimer's Disease Rating Scale (iADRS), a composite tool combining the Alzheimer's Disease Assessment

Scale-Cognitive subscale (ADAS-Cog13) and the Alzheimer's Disease Cooperative Study - instrumental Activities of Daily Living (ADCS-iADL) for function. Key secondary endpoints include changes between baseline and 76 weeks in the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog13), ADCS-iADL, MMSE, and Clinical Dementia Rating Scale Sum of Boxes (CDR-SB) scores. Other secondary biomarker endpoints include changes from baseline to week 76 in brain amyloid deposition and brain tau deposition and volumetric MRI. The safety, tolerability and efficacy of donanemab are also being evaluated in the ongoing randomized, placebo-controlled, double-blind, multi-center Phase 2 study TRAILBLAZER-ALZ 2 (NCT04437511).

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[3]. There are currently over 50 million people living with dementia around the world, with numbers expected to increase to nearly 152 million by 2050[4]. 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[5]. 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[4].

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 Lilly's Alzheimer's disease platform, including donanemab as a potential treatment for people with early symptomatic 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, or that donanemab will receive regulatory approval. 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. Mintun M, Lo AC, et. al. Donanemab Slows Progression of Early Symptomatic Alzheimer's Disease in Phase 2 Proof of Concept Trial. Presented virtually at the International Conference on Alzheimer's & Parkinson Diseases™ 2021 (AD/PD™ 2021); March 9-14.
2. Mintun M, Lo AC, et. al. (2021). Donanemab in Early Alzheimer's Disease. New England Journal of Medicine, https://www.nejm.org/doi/full/10.1056/NEJMoa2100708.
3. Alzheimer's Association. Facts and Figures. https://www.alz.org/alzheimers-dementia/facts-figures. Accessed December 8, 2020.
4. Alzheimer's Disease International. World Alzheimer Report 2019. https://www.alz.co.uk/research/WorldAlzheimerReport2019.pdf. Accessed December 8, 2020.
5. 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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