Lilly Provides Update on A4 Study of Solanezumab for Preclinical Alzheimer's Disease

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Results showed solanezumab did not slow cognitive decline in preclinical Alzheimer's disease or reduce risk of progression to symptomatic Alzheimer's disease

Solanezumab targets soluble amyloid beta, and treatment did not result in clearance of brain amyloid plaque

Lilly remains committed to fighting Alzheimer's disease, with plaque-clearing mechanisms such as donanemab and remternetug, both in ongoing Phase 3 trials

INDIANAPOLIS, March 8, 2023 /PRNewswire/ -- Eli Lilly and Company (NYSE:LLY) announced today that solanezumab did not slow the progression of cognitive decline due to Alzheimer's disease (AD) pathology when initiated in individuals with amyloid plaque but no clinical symptoms of the disease, known as the preclinical stage of AD[1]. Solanezumab only targets soluble amyloid beta. The treatment did not clear plaque or halt accumulation of amyloid in participants treated with the drug in the Anti-Amyloid Treatment in Asymptomatic Alzheimer's disease (A4) Study.

"Results of the A4 Study clearly showed that the primary and secondary endpoints were not met. Therefore, the A4 Study concludes our clinical development of solanezumab and indicates that targeting soluble amyloid beta through this mechanism is not effective in this population," said John Sims, head of medical, global brand development – solanezumab, for Eli Lilly and Company. "While this study was negative, the unique data generated have increased our understanding of preclinical Alzheimer's disease and will advance the next generation of AD prevention studies. Raw data and analyses will be made widely available to researchers through the public-private partnership with the NIH-funded Alzheimer's Clinical Trial Consortium. These data will serve the scientific community and enable Lilly and other drug developers to enhance our clinical trial designs for other potential medicines targeting Alzheimer's disease."

Launched in 2013, the A4 Study was a first-of-its-kind secondary prevention trial, enrolling more than 1,100 individuals between 65 and 85 years of age who had PET-imaging evidence of amyloid plaque accumulation in the brain and who did not have clinical impairment. Participants were randomized to either solanezumab or placebo and then treated for approximately 4.5 years.

Solanezumab binds only to soluble amyloid-beta protein and was not expected to significantly remove deposited amyloid plaques. Donanemab and remternetug, other Lilly investigational antibodies currently being developed in Phase 3, are different from solanezumab in that they specifically target deposited amyloid plaque and have been shown to lead to plaque clearance in treated patients.

More than 6.5 million Americans are currently suffering dementia due to Alzheimer's disease[2], and scientists expect this number to nearly triple by 2050[3]. It is estimated that more than 20 million Americans and approximately 315 million people globally have preclinical Alzheimer's disease, the earliest stages of the disease [4, 5].

During the double-blind portion of the study, results showed:

- Solanezumab did not slow cognitive decline on the primary outcome measure, the Preclinical Alzheimer Cognitive Composite (PACC) [mean change (95% CI): placebo -1.4 (-1.76, -1.04); solanezumab -1.69 (-2.13, -1.26); p-value 0.26)]. The PACC was developed to measure the aspects of cognitive decline relevant in preclinical AD and is an equally weighted composite that tests episodic memory, timed executive function, and global cognition.
- Secondary clinical outcome results were consistent with the primary outcome, numerically favoring placebo compared with solanezumab.
- 36.1% of participants starting at the stage of preclinical AD progressed on the Clinical Dementia Rating-Global Scale (defined as CDR-global score greater than 0 at two consecutive visits or final visit). CDR-GS is a clinician-rated scale that provides an overall assessment of the participant's clinical stage of AD. Similar rates of progression were seen with both the solanezumab and placebo groups.
- On amyloid PET imaging, amyloid continued to accumulate over time in both the placebo (65.9 Centiloid baseline, 17.5 Centiloid increase) and solanezumab (66.2 Centiloid baseline, 12.1 Centiloid increase) groups.
- Higher baseline amyloid levels were strongly associated with a greater risk of progression to symptomatic Alzheimer's disease (p-value<0.001).
- The solanezumab and placebo groups were well-balanced at baseline, and results were consistent across multiple analysis methods and models.
- Safety results in the A4 Study were consistent with the safety profile observed in previous solanezumab Phase 3 studies. Amyloid-Related Imaging Abnormalities with edema/effusion (ARIA-E) were uncommon and similar between treatment and placebo groups.

"These findings indicate that amyloid is a key driver of cognitive decline at the preclinical stage of Alzheimer's disease. Solanezumab did not substantially impact amyloid plaque burden in the brain, and unfortunately did not slow cognitive decline. These data suggest that we may need to be more aggressive with amyloid removal even at this very early stage of disease," said Reisa Sperling, M.D., a neurologist at the Brigham and Women's

Hospital, Harvard Medical School and the A4 Study project director. "We are so very grateful to the participants, their study partners, the clinical trial site investigators and staff, and the entire study team for their longstanding dedication to this important study. It is imperative that we learn everything we can to inform ongoing and future trials in our quest to prevent memory loss due to Alzheimer's disease."

The A4 Study is a landmark public-private partnership, funded by the National Institute on Aging (part of National Institutes of Health), Eli Lilly and Company, Alzheimer's Association, GHR Foundation, Foundation for the National Institutes of Health, and several other organizations and donors. The A4 Study is coordinated by the Alzheimer's Therapeutic Research Institute (ATRI) at the Keck School of Medicine of University of Southern California and is a project of the Alzheimer's Clinical Trials Consortium (ACTC).

Full disclosure of the study results will be shared later in the year at a scientific conference.

About the A4 Study
The Anti-Amyloid Treatment in Asymptomatic Alzheimer's disease (A4) Study is a Phase 3, double-blind, placebo-controlled study in males and females ages 65 to 85 years with preclinical AD (that is, in individuals with evidence of brain amyloid pathology on PET amyloid imaging who are clinically unimpaired but at high risk for cognitive decline).

The A4 Study tested whether solanezumab could slow the progression of Alzheimer's disease-related cognitive decline, brain imaging, and other biomarkers over the course of approximately 4.5 years. The study included more than 1,100 participants at 67 sites throughout the United States, Japan, Canada and Australia.

About Lilly
Lilly unites caring with discovery to create medicines that make life better for people around the world. We've been pioneering life-changing discoveries for nearly 150 years, and today our medicines help more than 47 million people across the globe. Harnessing the power of biotechnology, chemistry and genetic medicine, our scientists are urgently advancing new discoveries to solve some of the world's most significant health challenges, redefining diabetes care, treating obesity and curtailing its most devastating long-term effects, advancing the fight against Alzheimer's disease, providing solutions to some of the most debilitating immune system disorders, and transforming the most difficult-to-treat cancers into manageable diseases. With each step toward a healthier world, we're motivated by one thing: making life better for millions more people. That includes delivering innovative clinical trials that reflect the diversity of our world and working to ensure our medicines are accessible and affordable. To learn more, visit Lilly.com and Lilly.com/newsroom or follow us on Facebook, Instagram and LinkedIn. C-LLY

This press release contains forward-looking statements (as that term is defined in the Private Securities Litigation Reform Act of 1995) about A4 Study results, the conclusion of Lilly's clinical development of solanezumab, and regarding other Lilly product candidates, and reflects Lilly's current beliefs and expectations. However, there are substantial risks and uncertainties in the process of drug research, development, and commercialization. For a discussion of risks and uncertainties that could cause actual results to differ from Lilly's expectations, 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. Sperling, Aisen, et al Alzheimer & Dementia 2011.
2. Centers for Disease Control and Prevention. Alzheimer's Disease. Available at: https://www.cdc.gov/dotw/alzheimers /index.html#:~:text=Alzheimer%27s%20disease%20is%20the%20most,of%20death%20for%20all%20adults. Accessed November 9, 2022.
3. Alzheimer's Disease International. Dementia Statistics. https://www.alzint.org/about/dementia-facts-figures/dementia-statistics/. Accessed November 9, 2022.
4. Brookmeyer, R. et al. "Forecasting the prevalence of preclinical and clinical Alzheimer's disease in the United States." Alzheimer's & Dementia 14 (2018) 121-129.
5. Gustavsson, A. et al. "Global estimates on the number of persons across the Alzheimer's disease continuum." Alzheimer's & Dementia (2022) 1-13.

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