# A4 Study Results: Investigational Anti-Amyloid Treatment Started Before Alzheimer's Symptoms Did Not Slow Memory Loss

## Topline results announced from international clinical trial to prevent Alzheimer's disease symptoms led by Brigham and Women's Hospital principal investigator Reisa Sperling, MD

Preliminary results from a landmark clinical trial to prevent Alzheimer's disease (AD) symptoms show that an investigational anti-amyloid drug, solanezumab, did not demonstrate a statistically significant slowing of cognitive decline associated with AD when initiated prior to the stage of clinical impairment. The Anti-Amyloid Treatment in Asymptomatic Alzheimer's study ("A4 Study") was funded as a public-private partnership by the National Institute on Aging, part of the National Institutes of Health (NIH); Eli Lilly and Company; Alzheimer's Association; GHR Foundation; Foundation for the NIH; and several other organizations and donors. The A4 Study is coordinated by the Alzheimer's Therapeutic Research Institute at the Keck School of Medicine of USC and is an affiliated project of the Alzheimer's Clinical Trials Consortium. The A4 Study was led by co-principal investigator Reisa Sperling, MD, Director of the Center for Alzheimer Research and Treatment at Brigham and Women's Hospital, a founding member of the Mass General Brigham healthcare system.

"Unfortunately, the results from our study did not show evidence that treatment with solanezumab slowed cognitive or functional decline at the preclinical stage of AD," said Sperling. "We are very disappointed for our participants and their families, as well as the hundreds of people who worked on this study for almost a decade, but we will learn a great deal from this work that will inform ongoing and future trials."

No statistically significant difference was observed between solanezumab and placebo groups 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). Secondary outcome results were consistent with the primary outcome, with all clinical outcomes numerically favoring placebo compared with solanezumab. Longitudinal amyloid PET imaging demonstrated that amyloid continued to accumulate over time in both 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).

Working closely with her co-principal investigator, Paul Aisen, MD, from University of Southern California, Sperling and the A4 Study team screened over 6,800 participants, recruited from the Brigham and 66 other sites across the United States, Canada, Japan and Australia. Over 1,150 eligible participants, ranging from 65 to 85 years of age who had normal thinking and memory ability but evidence of elevated amyloid plaque accumulation—a build-up of protein in the brain, were randomized into the A4 Study treatment trial. The researchers used an imaging test called a PET scan to determine whether a potential participant had evidence of amyloid plaque buildup, which begins many years before symptoms of AD appear and is thought to confer high risk of cognitive decline. Participants were randomized to receive a placebo or the investigational antibody,

solanezumab, which binds to soluble forms of amyloid. The study was double blinded, meaning neither patients nor researchers knew which individuals received the treatment. Participants were studied for four and a half years in the double-blind phase with longitudinal cognitive testing, blood, and imaging measures.

“We did observe clear evidence that greater amyloid burden at baseline was associated with more rapid decline in the A4 Study. More than one-third of the participants progressed to a stage of clinical impairment over the study, driven by the group who started with the highest levels of amyloid,” Sperling said. “Unfortunately, solanezumab did not substantially impact the levels of amyloid plaque in the brain and did not slow cognitive decline. These findings suggest that we likely need to be more aggressive with amyloid reduction even at this very early stage of disease, as we are testing in the AHEAD 3-45 Study.”

In the AHEAD 3-45 Study, Sperling and colleagues are testing lecanemab, a different anti-amyloid antibody, through a public-private partnership with funding from NIH to the Brigham and Eisai and Co. Lecanemab demonstrated amyloid reduction and positive clinical results in a later stage of symptomatic AD in the Clarity AD study. The AHEAD Study is testing lecanemab at the stage of preclinical AD.

“The A4 Study was successful in demonstrating the feasibility of conducting a large-scale trial in people with evidence of amyloid in their brain who do not yet have symptoms, and we are so grateful to our very dedicated participants,” Sperling said. “As we continue to analyze the data, we expect to learn much more about the factors that influence the rate of progression towards Alzheimer’s disease dementia.”

In a companion study to A4 called Longitudinal Evaluation of Amyloid Risk and Neurodegeneration (LEARN), Sperling and colleagues are also following a group of individuals who do not yet show evidence of amyloid buildup.

The A4 and LEARN studies incorporated innovative additional methods to track early decline, building on research conducted at Mass General Brigham in the Harvard Aging Brain Study demonstrating that clinically normal individuals with signs of amyloid plaque buildup showed evidence of subtle abnormalities in brain function and increased risk of cognitive decline, using sensitive pencil and paper tests. The primary endpoint for the A4 Study was a composite of tests that measure and track the earliest signs of a decline from “normal” to subtly abnormal cognitive performance. A4 was powered to detect a treatment effect of approximately 30 percent slowing of the rate of cognitive decline.

Other novel measures were developed for the A4 Study that are now being utilized in other Alzheimer prevention trials. Sperling and her colleagues, Dorene Rentz, PsyD, of BWH and MGH, and Kathryn Papp, PhD, of BWH, created a new test for memory of names and faces to detect very early memory changes. Participants completed these memory tests, using an iPad, every six months to investigate changes in computerized cognitive testing over time. PET scans that can detect the other hallmark pathology of Alzheimer’s disease, tau tangles, known as Tau PET, was introduced into the A4 Study, largely based on work by Keith Johnson, MD, of MGH, in the Harvard Aging Brain Study.

Sperling says that this approach draws on successful methods used with other chronic diseases.

“The approach we took for the A4 Study is inspired by the way we treat heart disease, diabetes, and cancer,” she said. “We’ve made such strides in these diseases by identifying people who have evidence of heightened risk or silent disease detected by screening and initiating treatment before they show any clinical symptoms of the disease.”

All of the screening data for the A4 Study and LEARN were shared broadly with the Alzheimer's disease field, and the full longitudinal dataset, including cognitive outcomes, images, and biospecimens will be shared through the Alzheimer's Clinical Trial Consortium. This information will be used to inform ongoing trials and design future studies to prevent the symptoms of Alzheimer's disease with other promising investigational agents.