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## **New Data Shows Combination Therapy is More Effective than Monotherapy in Removing Beta-Amyloid Plaques from the Brains of Mice**

### **Study Results Presented at the Alzheimer's Association International Conference 2014**

INDIANAPOLIS, July 13, 2014 /PRNewswire/ -- Eli Lilly and Company (NYSE: LLY) today announced results from its non-clinical study in genetically engineered mice examining combination therapy with the murine version of the beta-amyloid antibody N3pG and beta-secretase inhibitor BACE (LY2811376). Data results found that combination therapy was more effective in removing clumps of amyloid-beta protein in the brain - a component that is thought to lead to Alzheimer's disease (AD) - than use of one therapy. These data were presented today at the Alzheimer's Association International Conference 2014 (AAIC 2014) in Copenhagen, Denmark by Ron DeMattos, Ph.D., research fellow in the Neuroscience Division at Eli Lilly and Company. The data was also featured by the AAIC in a research media tips sheet.

"This non-clinical study demonstrates that by simultaneously targeting two different steps in the beta-amyloid disease process, researchers can slow the progression of Alzheimer's disease pathology in genetically engineered mice," said Dr. DeMattos. "These results may have a significant impact on the future of Alzheimer's disease therapies as they support the clinical rationale for using future testing of combination therapy against the a-beta protein in the clinical practice."

Alzheimer's disease, the most common form of dementia, causes progressive decline in memory and other aspects of cognition. A number of new investigational mechanisms for the treatment of Alzheimer's disease are currently in development. One type of investigational mechanism, called beta-secretase inhibitors, aims to block the body's ability to produce beta-amyloid protein, a possible component that leads to Alzheimer's disease. The other type of investigational drug is called a beta-amyloid antibody, which targets the removal of the beta-amyloid protein. Compounds that are thought to work through these mechanisms have been studied in clinical trials on their own; however, most of the trials have not shown significant treatment effects. Therefore, many believe that multiple steps of the beta-amyloid deposition process need to be simultaneously targeted in order to remove significant quantities of the beta-amyloid pathology.

The non-clinical study results showed that when used on their own (as monotherapies), the beta-secretase inhibitor and the N3pG beta-amyloid antibody removed approximately 50 percent of the clumps of amyloid-beta protein, whereas the combination therapy resulted in an even more substantial 86 percent removal. Additionally, combination therapy significantly lowered deposited A $\beta$ 1-42 75 percent relative to the time zero controls. Histological analyses indicated that the BACE inhibitor monotherapy resulted in removal of diffuse deposits of beta-amyloid, the antibody monotherapy resulted in removal of cored plaques, and the combination therapy removed both the diffuse deposits and cored plaques. Multiple different types of biochemical analyses confirmed that the combination treatment was superior to the monotherapy treatments.

### **Study Methods**

Aged PDAPP transgenic mice (17-19 months) were randomized into the following five cohorts: 1) time zero control, 2) large and small molecule compound controls, 3) plaque-specific A $\beta$  antibody (anti-A $\beta$ p3-x), 4) BACE inhibitor, and 5) A $\beta$  antibody + BACE inhibitor. The aged mice were treated for four months with either a beta-secretase inhibitor or the N3pG beta-amyloid antibody, or the combination of the two drugs. Effectiveness of the treatments was determined by measuring the amount of beta-amyloid protein remaining in the brains of the mice.

### **About Alzheimer's Disease**

Alzheimer's disease is a fatal illness that causes progressive decline in memory and other aspects of cognition.<sup>1</sup> It is the most common form of dementia, accounting for 60 to 80 percent of dementia cases.<sup>1</sup> There are currently an estimated 44 million people living with dementia worldwide.<sup>2</sup> The number of people affected by dementia is expected to be more than 75 million in 2030 and 135 million in 2050.<sup>2</sup>

### **About Eli Lilly and Company**

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<sup>1</sup> Alzheimer's Association. 2014 Alzheimer's Disease Facts and Figures. [http://www.alz.org/downloads/facts\\_figures\\_2014.pdf](http://www.alz.org/downloads/facts_figures_2014.pdf). Accessed on June 4, 2014.

<sup>2</sup> Alzheimer's Disease International. Policy Brief for Heads of Government: The Global Impact of Dementia 2013 - 2050. <http://www.alz.co.uk/research/GlobalImpactDementia2013.pdf>. Published December 2013. Accessed on June 4, 2014.



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