



## IS THERE A ROLE FOR BACE INHIBITION IN ALZHEIMER'S TREATMENT?

Barcelona, Spain. October 25, 2018. Beta-secretase (BACE) inhibitors emerged in recent years as one of the most promising classes of drugs for treatment of Alzheimer's disease (AD). However, disappointing results from a Phase 3 clinical trial presented at the Clinical Trials on Alzheimer's Disease (CTAD) meeting in Barcelona, Spain tempered some of the optimism surrounding BACE inhibition, and prompted investigators from multiple companies developing drugs in this class to come together and jointly examine the potential benefits and risks of BACE inhibition.

BACE1 is an enzyme that cleaves the amyloid precursor protein as the first step in the production of beta-amyloid, the protein that forms the characteristic plaques found in the brains of people with AD. In animal models of AD, BACE1 inhibition reduced production of beta amyloid, cleared plaques, and improved cognition. Among the many different BACE1 inhibitors in development, Merck's verubecestat is one of the most advanced. Last year, Merck terminated a study of verubecestat in mild to moderate AD when an interim analysis showed that the drug was ineffective at slowing the rate of cognitive decline. Reasoning that the drug might be more effective if given earlier in the disease process, before substantial build up of plaque, the company continued their trial in prodromal AD. But in February, 2018, the company stopped the trial after an independent data monitoring committee determined that there was no evidence of efficacy. Even more troubling, data presented at CTAD on Monday showed that verubecestat treatment was associated with worsening on all clinical measures and an increase in adverse effects, according to Michael Egan of Merck and Co. "This was very surprising and disappointing, but it's important to go through these results to see what we can learn."

These results raise many unanswered questions, said Paul Aisen, Director of the Alzheimer's Therapeutic Research Institute (ATRI) at the University of Southern California. For example, the rapid onset of cognitive worsening might be related to an effect of rapid lowering of beta amyloid on synaptic function, or to inhibition of BACE cleavage of a substrate other than APP, or to an off-target activity of the drug. These effects could be specific to verubecestat and a few other BACE inhibitors, or could involve the entire class. "These are all critically important questions," said Aisen.

Pierre Tariot of the Banner Health System in Phoenix, Arizona raised other key questions: is the negative effect related to dose, duration of treatment, or the specific population enrolled in the trial. For example, if the negative effects are reversible, changing the dosing regimen could mitigate the problem. Tariot added that when he called his patients who were participating in the trial to tell them the trial had been terminated, "they begged us not to overreact." They reminded him that AD is a terrifying prospect and that the adverse effects pale in comparison to the disease itself or to the side effects experienced by patients with other diseases such as cancer.

The best way to resolve these questions, said Aisen, is to openly share data from the many trials conducted by academic and industry scientists. To this end, the Alzheimer's Association sponsored an emergency session at CTAD to explore emerging results from other BACE inhibitor trials. Gary Romano of Janssen presented data from the EARLY trial of atabecestat in preclinical AD, which was terminated in May, 2018 because of elevations in a liver enzyme seen in about a third of patients. Although the levels returned to baseline, Janssen determined that the benefit risk profile of the drug was not appropriate for a preventive treatment. A preliminary analysis of data from the study suggested that there may have also been a dose-related worsening on cognitive measures.

From Eli Lilly and Company, Albert Lo presented data from a Phase 2 study of the BACE inhibitor LY3202626, another study that was terminated early due to a low probability of success. Eisai/Biogen and Novartis/Amgen also shared preliminary data from studies that are ongoing. Importantly, many of these trials have collected rich biomarker and imaging data, which will be analyzed in the coming months along with cognitive and clinical data to see what else can be learned. Reisa Sperling, of the Brigham and Women's Hospital and Harvard Medical School in Boston and co-principal investigator (with Aisen and Ron Petersen) of the newly formed Alzheimer's Clinical Trials Consortium (ACTC) suggested that the consortium could serve as a neutral party to analyze data across multiple studies.

Maria Carrillo, Chief Science Officer of the Alzheimer's Association added that the Association will be leading conversations in the coming months to explore what can be gleaned from these data in order to inform ongoing and future studies. "We need to maximize every opportunity for success," she said. "Only together will we be able to advance this field. Our patients are waiting."

In a separate symposium on Thursday, Randall Bateman of Washington University in St. Louis, Missouri chaired a panel exploring whether BACE1 is a suitable drug target for the prevention and treatment of AD. Stefan Lichtenthaler of the German Center for Neurodegenerative Diseases suggested that the disappointing results of many of the BACE inhibitor trials could be related to treatment starting too late or using doses that are too high. "By taking these extra steps and finding the right dose, I feel that BACE1 can still be an excellent target for preventing AD," he said.

Eric McDade from Washington University added that BACE1 inhibition may be ideal for primary prevention and that dominantly inherited AD is a predictable model in which to study such interventions. The Dominantly Inherited Alzheimer's Network (DIAN) study has shown that amyloid accumulation becomes significant as much as 15 years before symptoms appear in people with autosomal dominant forms of AD, which gives investigators the opportunity to decide when and how to intervene using adaptive designs. "It's imperative that we really dig into this," said McDade.

