Novel, Oral Drug TTP488 Shows Promise for Disease Modification in Alzheimer's Patients

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A novel, orally administered drug candidate, TTP488, has demonstrated clinical evidence of slowing of cognitive decline over 18 months of therapy in patients with mild to moderate Alzheimer's disease. TTP488 is a small-molecule drug that is the first to show clinical benefit from research on the receptor for advanced glycation endproducts (RAGE), a new biochemical target in Alzheimer's disease treatment. TransTech Pharma, Inc. of High Point, North Carolina discovered, developed and owns all rights to this drug candidate.

These new clinical results arise out of a trial sponsored by Pfizer, Inc., and conducted by the Alzheimer's Disease Cooperative Study, a national research consortium funded by the National Institute on Aging, a part of the National Institutes of Health. The trial involved 399 patients with mild to moderate Alzheimer's disease at over 40 of the country's leading teaching hospitals involved in Alzheimer's research.

Analysis, by TransTech Pharma and third-party experts, of the study data reveals a 26% benefit relative to placebo in cognitive decline over 18 months in the group that received a 5 mg dose of TTP488. A more pronounced effect was observed in subjects with mild Alzheimer's disease, who showed a 46% benefit over placebo.

"At present, no FDA-approved drug has been shown to stop, prevent or alter the course of cognitive decline in patients with Alzheimer's disease," said Dr. Adnan Mjalli, Chairman and Chief Executive Officer of TransTech Pharma. "We are very excited about this data, which may lead to an approvable, novel treatment for millions of patients suffering from Alzheimer's disease here in the United States and around the globe. Because demand remains high for a treatment that can preserve cognitive function in this population, TransTech Pharma will be exploring options for accelerated FDA approval of this novel Alzheimer's treatment."

Dr. Mjalli added his thoughts concerning the drug's novel target, RAGE. "Exploiting the RAGE pathway offers a completely new approach to the treatment of Alzheimer's disease. Mechanistically, TTP488 acts, in part, by restoring the normal balance of amyloid protein transport into and out of the brain. Restoring this natural balance in patients with Alzheimer's disease, who have diminished capacity to clear amyloid protein from the brain, may result in long-term disease modification and maintenance of cognitive function."

"Given the recent failure of bapineuzumab and the inconclusive results of solanezumab, TTP488 is emerging as a promising new drug for the treatment of Alzheimer's disease in clinical development. RAGE antagonists have been of interest for some time. These exciting phase IIb results of TTP488 on top of optimal standard background therapy are encouraging and, with further study, could lead to a new treatment for Alzheimer's disease," commented Marwan Sabbagh MD, FAAN, Director, Banner Sun Health Research Institute, Research Professor of Neurology, University of Arizona College of Medicine-Phoenix and participating investigator in the TTP488 study.

"We are encouraged by the results of this study," said Cesare Orlandi, MD, Senior Vice President and Chief Medical Officer of TransTech Pharma. "Statistical analysis of the data from this study, including execution of the pre-specified primary analyses following regulatory standards, resulted in significant p-values. Extensive post-hoc analyses also revealed a consistent signal indicative of a therapeutic benefit at the 5 mg dose level involved in this study. The magnitude of the observed effect in the subpopulation suffering from mild Alzheimer's disease is of particularly great interest. This finding will allow us to optimize the design of future studies."

TransTech Pharma believes that the benefits observable in the data collected in the clinical trial did not support the decision by Pfizer, Inc., to halt the trial prior to its intended completion. For example, although individuals enrolled in the trial at the highest tested dose experienced signs of toxicity, those effects were reversible, and the lower dose resulted in the benefits and lack of adverse events reported here.

Douglas Galasko, the principal investigator at the University of California, San Diego, for the Alzheimer's Disease Cooperative Study, suggested "Stopping the study early in accordance with a pre-specified futility analysis may have been premature. In light of the benefit of low dose TTP488 on cognitive decline important additional data could have been collected."

Technical Analyses of the Trial

The pre-specified intent to treat analysis of the primary endpoint, ADAS-cog11, and relative sensitivity analyses showed statistically significant benefit at month 18 of TTP488 5 mg once daily over placebo. A 26% reduction in decline in ADAS-cog11 scores over placebo was observed in the group receiving TTP488. A more pronounced effect was observed in subjects with mild Alzheimer's disease with a 46% reduction in decline over placebo, during the course of the study suggesting a benefit of starting therapy in patients with milder disease. Statistically significant differences in ADAS-cog11 beginning at month six and continuing through month eighteen were observed in pharmacokinetic/pharmacodynamic data (PK/PD) analyses of the entire population having trough plasma concentrations in an optimal range. Regardless of how progression in Alzheimer's disease is defined based on change in ADAS-cog score, the progression tended to be less in subjects treated with TTP488 than in subjects treated with placebo.

At an oral daily dose of 5 mg, TTP 488 administration was safe and well tolerated. No significant differences in cardiovascular events were observed between TTP488 and placebo-treated subjects. No cases of vasogenic edema or parenchymal hemorrhage were reported in TTP488-treated subjects. TTP488 treatment resulted in a statistically significant decrease in the incidence of psychiatric adverse events. A slower onset of adverse events of special interest for Alzheimer's disease patients, including falls, confused state, somnolence and dizziness, was also observed in the TTP488-treated subjects.

About TTP488

Substantial data suggest that RAGE is involved in the pathogenesis of Alzheimer's disease, and that sustained amyloid beta interaction with RAGE on blood-brain barrier (BBB) and/or neuronal cells and/or microglial cells is an important element of amyloid plaque formation and chronic neuronal dysfunction.

TTP488 is a novel, small-molecule, orally active antagonist of RAGE. TransTech Pharma discovered and developed TTP488 using its proprietary drug discovery platform TTP Translational Technology®. Administered once daily in animal models, TTP488 inhibited amyloid plaque formation and inflammation resulting from the binding of amyloid beta protein and other RAGE-ligands to RAGE. TTP488 also reduced amyloid load in the brain and improved cognitive performance in transgenic APP mice.

About Alzheimer's Disease

Alzheimer's disease, the most common form of dementia, is a progressive neurodegenerative disorder that causes decline in cognition and functional abilities. It has been estimated to affect 5 million individuals in the United States, and represents the 6th leading cause of death. Worldwide there are currently 35.6 million people with dementia, and the number is estimated to increase to over 115 million by 2050.

While current approved therapies for Alzheimer's disease focus on improving the symptoms of the cognitive dysfunction, there is currently no treatment to slow disease progression.

About TransTech Pharma

TransTech Pharma is a privately held, clinical-stage pharmaceutical company focused on the discovery, development, and commercialization of human therapeutics to fill unmet medical needs. The Company's high-throughput drug discovery platform, Translational Technology®, translates the functional modulation of human proteins into safe and effective medicines. TransTech Pharma has a pipeline of small-molecule clinical and pre-clinical drug candidates for the treatment of

a wide range of human diseases, including central nervous system disorders, diabetes, obesity, cardiovascular disease, inflammation and cancer. For further company information, visit http://www.ttpharma.com.

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