Positive Data Released for Alzheimer’s Gene Therapy Approach

Sangamo BioSciences, Inc. has announced positive findings from the Phase I clinical trial of CERE-110 (AAV-NGF) for the treatment of Alzheimer’s disease (AD). CERE-110 is an adeno-associated viral (AAV) vector that encodes the gene for nerve growth factor (NGF).

Ten participants with mild to moderate AD were treated with a single administration of CERE-110 in an open-label dose-escalation study to evaluate three different doses of the therapeutic agent. The drug was delivered by standard stereotactic surgery into the nucleus basalis of Meynert (NBM), and participants were followed for 24 months. The trial was designed to evaluate safety and tolerability, as well as signs of efficacy.

The data demonstrated that:
- The treatment is feasible and well tolerated. Serious adverse events (AEs) were transient, acceptable, and related to the surgical procedure. AEs were not dose-related and not related to either the AAV or NGF.
- Long-term expression of NGF, a naturally occurring protein that maintains survival of nerve cells in the brain, was observed in brain tissue, with desired changes in neuronal cell volume of targeted neurons providing evidence of bioactivity.
- Preservation of glucose utilization, as measured by 18FDG (fludeoxglucose) positron emission tomography brain imaging, was observed through the 24 months of the study, suggesting that the nerve cells of the brain were not deteriorating significantly over this time period.
- Efficacy assessments such as mental state, cognition, and activities of daily living demonstrated no evidence of accelerated decline over 24 months, although the sample was too small to allow any conclusions to be drawn regarding improvement in symptoms.

CERE-110 is surgically injected into the NBM, a brain region where cholinergic nerve cell degeneration occurs in AD. Delivery of NGF using an AAV vector has the potential to induce sustained expression of NGF, resulting in long-lasting protection and preservation of cholinergic nerves. A Phase II trial involving 49 patients with mild to moderate AD is currently under way.

First Human Trial of Selective Muscarinic M1 Receptor Agonist for Alzheimer’s Disease Initiated

Heptares Therapeutics has initiated its Phase I clinical study of HTL9936, an orally available, small molecule drug candidate. It is the first fully selective muscarinic M1 receptor agonist to enter clinical development. Heptares plans to develop HTL9936 as a novel treatment for improving cognitive function in patients with Alzheimer’s disease and other diseases associated with dementia and cognitive impairment.

Researchers will evaluate the safety, tolerability, and pharmacokinetics of HTL9936, as well as investigate the drug’s clinical pharmacodynamics. The study aims to recruit more than 100 healthy volunteers, including older adults, at a clinical center in the United Kingdom.

M1 receptor agonism is a well-validated mechanism of action for treating cognitive impairment and a valuable pharmacological profile that the pharmaceutical industry tried to create for decades. The principal challenge has been to engineer selective compounds that activate the M1 receptor subtype without also activating the M2 or M3 receptors, which are associated with undesirable side effects. All previous compounds have been discontinued due to inadequate selectivity.

However, using a new structure-guided approach, Heptares scientists determined the x-ray crystal structure of the M1 receptor for the first time and identified new chemistries with fully selective M1 agonist profiles. Phase I results are expected in mid-2014.