CERE-120 for Parkinson's Disease

Scientific Abstract

Parkinson's disease (PD) is a progressively debilitating neurodegenerative disorder that currently afflicts over one million people in North America. Cardinal symptoms of PD include resting tremor, rigidity, bradykinesia and postural instability. Although its etiology is unknown, the pathogenesis of PD involves the progressive loss of function, and eventual death of substantia nigra dopaminergic neurons that project to basal ganglia structures, in particular the striatal regions including the caudate and putamen. The dopamine precursor, levodopa (L-Dopa), is the standard of care of therapy for PD, and acts by improving dopaminergic function of the degenerating nigrostriatal cells. While L-Dopa offers palliative treatment for symptoms, it does not retard progression of the disease. Moreover, over time the effectiveness of L-Dopa gradually declines, narrowing the therapeutic index, and leading to the emergence of serious L-Dopa induced dyskinesias. Striatal dopamine levels and levels of the dopamine synthesizing enzyme, tyrosine hydroxylase, may be reduced by *as* much as 80% when parkinsonian symptoms first appear. However, the loss of nigral neurons and nigrostriatal terminals appears to be far less severe, with only a 30-50% reduction at symptomatic onset. The population of nigrostriatal neurons that are structurally intact but have lost phenotypic dopamine expression represents a clear therapeutic target for restoration and protection.

Several proteins known as neurotrophic or growth factors can augment the function of nigrostriatal dopaminergic neurons and protect them from degeneration. Glial cell line-derived neurotrophic factor (GDNF) and neurturin (NTN) are two of these well-characterized factors. NTN is a naturally-occurring functional and structural analog of GDNF. There have been numerous studies conducted which have demonstrated the comparable beneficial effects of GDNF and NTN in animal models of PD. In addition, clinical studies have been conducted that have also evaluated the safety of GDNF administered directly into the brain of PD patients.

To be safe and effective, neurotrophic factor therapy should cover as much of the target area with the therapeutic protein as possible without affecting non-target sites. Gene transfer confers the ability to have a protein such as NTN produced *in situ*, precisely in and without substantial distribution beyond the nigrostriatal target, following a single neurosurgical procedure. For many indications, adeno-associated virus serotype 2 (AAV2) has emerged as the optimal vector for gene transfer. AAV2-based gene transfer vectors are currently being tested in human clinical studies, including several utilizing gene transfer to the central nervous system. To date, AAV2-based vectors appear to be safe.

Thus, targeted delivery of NTN to nigrostriatal neurons using an AAV2-based vector could be a safe and effective treatment for PD. In non-clinical studies, the AAV2-based vector encoding NTN, known as CERE-120, has been shown to effectively deliver the neurotrophic factor to the nigrostriatal system and protect nigral dopaminergic neurons from degeneration in both rodent and non-human primate models of PD. In addition, extensive rodent and non-human primate safety/toxicity studies have shown that administration of CERE-120 to the striatum is safe and well tolerated.

In 2005, a Phase 1 clinical study entitled "*A Phase I, Open-Label Study of CERE-120 (Adeno-Associated Virus Serotype 2 [AAV2]-Neurturin [NTN] to Assess the Safety and Tolerability of Intrastriatal Delivery to Subjects With Idiopathic Parkinson's Disease*" was initiated (RAC Protocol #0501-689, FDA BB-IND 12199). The study investigated the safety and tolerability of CERE-120 administration to the nigrostriatal system of 12 subjects with moderate to advanced Parkinson's disease (6 subjects for each of two CERE-120 doses tested). The first subject was administered CERE-120 in June 2005, and the last subject in March 2006. Thus, safety assessments on patients now range from 4 to 12 months post-administration (9 to 12 months for low dose; 4 to 8 months for high dose). To date, no serious adverse events related to

CERE-120 or the surgery have been observed. No clinically significant adverse changes were observed on neuropsychiatric measures, physical or neurological examinations, or clinical laboratory test results. All subjects exhibited improvement in their total Unified Parkinson's Disease Rating Scale (UPDRS) scores as well as their UPDRS motor subscale scores recorded in the practically defined off condition (UPDRS-off; measured approximately 12 hours after the subject's previous dose of antiparkinsonian medication). An independent Data Safety Monitoring Board (DSMB) reviewed the data monthly over the course of the study, and each time concluded that the study should continue as planned. In June 2006, the DSMB conducted a review of all safety data including safety observations for at least 3 months for all patients. They concluded that the Phase I study had met its stated primary endpoint, which was demonstration of safety and tolerability of CERE-120 for the 3-month period post-administration.

Given the safety of CERE-120 observed in the Phase 1 clinical trial and the potential for CERE-120 to benefit subjects with PD, a double-blinded sham-controlled Phase 2 trial to assess the efficacy of CERE-120 in moderate to advanced PD, entitled "*Multicenter, Randomized, Double-Blind, Sham Surgery-Controlled Study of CERE-120 (Adeno-Associated Virus Serotype 2 [AAV2]-Neurturin [NTN]) to Assess the Efficacy and Safety of Bilateral Intraputaminal (IPu) Delivery in Subjects With Idiopathic Parkinson's Disease*", is now proposed. The study will examine 51 subjects with PD, randomized at a 2:1 ratio of CERE-120 to sham surgery. A single dose level of CERE-120, 5.7×10^{11} vector genomes, which is the higher of the two doses in the Phase 1 study, will be tested. Sham surgery will consist of partial burr holes into the skull, appearing to the subject and physician equivalent to those used to administer CERE-120, but with no breach of the inner surface of the skull. As a double-blind study, each subject, as well as the physicians performing their assessments, will not know their treatment group.

To be eligible, subjects must have bilateral idiopathic PD of at least 5 years duration since diagnosis, with motor fluctuations despite adequate oral antiparkinsonian medication. Subjects will be males or non-pregnant females 35 to 75 years of age, inclusive, at randomization. Subjects will have a UPDRS motor subscale score of 30 or greater in the practically defined off condition, and will demonstrate stability of parkinsonian features, stable medication requirements, and clear response to antiparkinsonian medications during the 30-day eligibility evaluation period. Subjects must provide signed informed consent before any study-specific procedure is performed.

The primary objective of the trial is to evaluate the efficacy of bilateral intraputaminal CERE-120 administration. Efficacy will be assessed by comparing the change from baseline in UPDRS motor score in the practically defined off condition between CERE-120 and sham surgery at 9 months post-administration. Secondary and other objectives include comparisons of UPDRS-off at shorter time points, UPDRS following the usual morning dose of antiparkinsonian medication (UPDRS-on), Individual UPDRS Mentation, Behavior and Mood, Activities of Daily Living, Complications of Dopaminergic Therapy for PD scores, timed motor tests, diary ratings regarding time "off" and "on" with or without dyskinesias, patient-reported outcome measures, investigator- and subject-rated clinical global impression ratings and concomitant antiparkinsonian medications. Approximately 20 subjects, at the same 2:1 ratio of CERE-120:sham will undergo fluorodopa positron emission tomography (PET) scans at baseline and 9 months post-administration to assess functional changes anatomically. Safety and tolerability will be further examined by thorough clinical evaluations, spontaneous adverse event reports, laboratory test results, neuropsychometric tests, and changes in cranial magnetic resonance imaging (MRI). Serum antibodies to AAV2 and NTN will be assessed at baseline, and at 1, 3, 6, and 9 months post-administration. An independent DSMB will review safety data at selected intervals, and at other times as necessary, during the course of the study. Long-term follow-up will consist of annual life-long evaluations.