**CERE-120 for Parkinson's Disease**

**Non-Technical Abstract**

Parkinson's disease is a gradually debilitating neurodegenerative disorder that currently afflicts approximately over one million people in North America. Characteristic features of Parkinson's disease include trembling of hands, arms, and legs, stiffness of limbs and trunk, slowness of movement, and impaired balance and coordination. These movement-related symptoms of Parkinson's disease correspond with the progressive loss of function, degeneration, and death of nerve cells (neurons) in a region of the brain called the substantia nigra. Substantia nigra neurons normally coordinate muscle movement by releasing a signaling chemical called dopamine into other regions of the brain, notably the caudate and putamen. However, as substantia nigra neurons become sick and die in Parkinson's disease, dopamine is lost, and the disease worsens.

There is no cure for Parkinson's disease. Effective medications aim to temporarily replenish or mimic dopamine's actions. However, as the disease progresses, the drugs gradually lose their effectiveness and increasingly cause side effects such as uncontrollable movements. In advanced patients, surgery may be warranted when symptoms of the disease no longer respond to drugs. Importantly, no currently available therapy addresses the loss of function and progressive death of the dopamine neurons of the substantia nigra.

Neurturin (NTN) is a naturally occurring human protein that has been shown to improve the function and prevent the death of substantia nigra dopamine neurons in animal models of Parkinson's disease. Thus, NTN may benefit Parkinson's disease patients if delivered to the damaged and dying dopamine neurons in their brains. However, as a protein, NTN would not readily access the brain or the dopamine neurons if administered as a pill or injection, therefore delivery of NTN to the brain is a challenge. Gene transfer may be a safe and effective method to overcome this challenge. In gene transfer, DNA encoding a desired protein is transferred into cells in an area where that protein is needed. Those cells then use the DNA to make the needed protein for that area.

CERE-120 is a gene transfer vector engineered from a virus that naturally infects human cells but which does not cause disease, known as adeno-associated virus type 2 (AAV2). In CERE-120, all of the AAV2 genes have been removed and replaced with a gene to make NTN. Animal studies have shown that when CERE-120 is injected into brain regions affected in Parkinson’s disease where substantia nigra neurons release dopamine to affect movement, NTN is made and delivered to the substantia nigra neurons, enhancing their vitality and protecting them from dying.

CERE-120's safety profile was first demonstrated in extensive animal studies (which included hundreds of rats and dozens of monkeys) as a necessary prerequisite prior to CERE-120 administration in human subjects. Following regulatory review by the FDA and NIH RAC, a Phase 1 clinical study of CERE-120 in human subjects with Parkinson's disease was initiated. Twelve subjects were surgically administered CERE-120 into the putamen. Six subjects were administered a lower dose, and six subjects received a higher dose. The subjects receiving the lower dose have now been closely monitored for 9 to 12 months, and the higher dose subjects for 4 to 8 months. CERE-120 has been found to be safe and well tolerated in the 12 subjects who are participating in the Phase 1 study.

The primary goal of the Phase 1 study is to assess safety and tolerability. No serious adverse effects related to CERE-120, or the surgical procedure required to administer it, have occurred. Specifically, the Parkinson's disease patients that received CERE-120 have shown no clinically

significant adverse changes on neuropsychiatric measures, physical or neurological examinations, or clinical laboratory test results. All subjects have shown improvement in their movement abilities at a time when their dopaminergic medications have effectively worn off, approximately 12 hours after their last dose. In addition, most of the subjects have reported a substantial increase in the amount of time that their medications are providing benefit without causing uncontrollable movements (dyskinesias). An independent data safety monitoring board (DSMB) has regularly reviewed the data from the Phase 1 subjects, and each time the board has concluded that the study should proceed 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 1 study had met its stated primary endpoint, which was demonstration of safety and tolerability of CERE-120 for the 3-month period post-administration.

Because the safety and tolerability of CERE-120 in subjects with Parkinson's disease has been demonstrated in the Phase 1 study, and the potential for CERE-120 to provide benefit to patients with Parkinson's disease exists, a Phase 2 clinical study is now proposed. The purpose of the Phase 2 study is to evaluate whether CERE-120 provides benefit to treated subjects. Thus, a larger number of subjects will be studied, and CERE-120 will be compared to a control (placebo) treatment group. To make the study more scientifically rigorous, a randomized, double-blind placebo-controlled design will be utilized, whereby the subjects, as well as the doctors evaluating the subjects, will not know which treatment the subject has received.

The subjects in the Phase 2 study that are randomized to receive CERE-120 treatment will receive the same dosage as the CERE-120 high dose treatment group received in the Phase 1 study. The subjects that are randomized to receive control treatment will have sham surgery, in which the subject receives partial burr holes in the skull. The skulls of the control treated (sham surgery) subjects will look and feel the same as the skulls of the CERE-120 treated subjects. The sham surgery holes will not breach the inner surface of the skull or expose the outer covering of the brain (i.e., the dura), therefore minimizing risks.

A total of 51 subjects with Parkinson's disease will be enrolled in the Phase 2 study. Of these, 34 will receive CERE-120 and 17 will receive the sham surgery. The primary outcome to be compared between the two groups is motor function at 9 months after surgery, assessed at a time when dopaminergic medication has worn off ("UPDRS-off"). Secondary measures will include UPDRS-off at earlier time points, motor assessment when medication is active ("UPDRS-on") at several time points, assessments of behavior and mood, activities of daily living, dyskinesia ratings, patient-reported outcome measures, and patient and physician clinical global impression ratings. Safety will also be monitored through spontaneous adverse event reports, laboratory test results, neurological and psychological tests, and changes in magnetic resonance imaging (MRI). Subjects will be monitored for the development of antibodies to CERE-120 and/or NTN. Additionally, positron emission tomography (PET) scans will be performed in a subset of the subjects at baseline and 9 months post-administration to evaluate functional effects in the brain anatomically. An independent safety monitoring board will review safety data at selected intervals, and at any other times as necessary during the course of the study. Subjects will have annual life-long evaluations performed for long-term follow-up.