3. NON-TECHNICAL ABSTRACT

Giant Axonal Neuropathy (GAN) is a progressive degeneration of the central nervous system, characterized by loss of motor and sensory function, and brain atrophy. The disease leads to complete loss of movement and ventilator dependence before causing death typically by age 30. There is currently no established treatment for GAN. It is caused by mutations in the gigaxonin gene, which results in a loss of function of a protein needed for long-term nerve survival. The role of gigaxonin is to maintain the correct balance of certain structural components of nerves. In the absence of functional gigaxonin, these structural components accumulate and cause toxicity. Nerve cells within and around the spinal cord are particular susceptible to this damage. The damage to nerve cells in the spinal cord and brain results in the breakdown of communication between the central nervous system and the peripheral nervous system and results in nerve death. In terms of the patient health, this damage causes a progressive loss of control over the legs and arms, eventually leading to patients being wheelchair-bound and later quadriplegic before they succumb to the disease.

The rationale of this study is that GAN may be safely and effectively treated using a minimally invasive gene replacement procedure. Our plan is to deliver the gigaxonin gene to cells of the spinal cord and brain using a non-toxic viral delivery system (scAAV9) in order to produce gigaxonin in the patient's cells. Researchers have found that in cultured human cells and in mice that have GAN, introduction of a working copy of the gigaxonin gene restores the normal distribution of the structural proteins within cells that are a hallmark of the GAN pathology. Moreover, delivery of the gigaxonin gene into mice that have GAN has improved their motor function, even when the mice were treated after the onset of their disease symptoms. To test whether such a therapy might be relevant to humans, monkeys were injected with a similar recombinant virus that carries a gene (GFP) that will make cells turn green if the gene is successfully delivered. In the monkeys, a single injection of this viral vector into the cerebrospinal fluid surrounding the spinal cord resulted in widespread gene expression throughout the nervous system. This study demonstrated that the procedure would likely scale well to humans, suggesting that the encouraging results in mice might benefit patients with GAN.

This research project is defined as a "Phase I" trial because it aims primarily to test the safety of the procedure and product in humans. If enough cells are infected with a healthy copy of the GAN gene, we hypothesize that gigaxonin will reorganize the disordered structural proteins which are a hallmark of the disease. This is expected to restore function to dysfunctional axons, resulting in increased axonal transport, thus increasing communication between the central and peripheral nervous systems. We hypothesize that the introduction of functional gigaxonin to nerve cells in the central nervous system will slow, halt, or reverse the progression of the disease in humans.

The study is divided into three phases: pretreatment, surgery, and post-gene delivery phase. The pre-treatment and post-treatment phases involve testing in order to assess the safety and potential benefits of the product and procedure. The risks of this procedure include those related to the lumbar puncture surgical procedure and to the introduction of the full length gigaxonin gene using a viral delivery method.

There may be some benefit to society as a whole in expanding our knowledge about gene therapy, and more specifically patients with Giant Axonal Neuropathy. Other neurodegenerative disorders may benefit from the study or the knowledge gained through it.