Gene therapy shows significant improvement in Parkinson's disease

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Neurologix, Inc. today announced the publication in the June 23 issue of the journal *The Lancet* of positive results from the first ever gene therapy trial for Parkinson's disease and the first report of direct gene transfer into a patient's own brain cells for any adult neurodegenerative disease.

The open label Phase 1 study, conducted in 12 patients with advanced Parkinson's disease demonstrated both a lack of adverse events related to the gene therapy procedure and statistically significant improvements from baseline in both clinical symptoms and abnormal brain metabolism (as measured by positron emission tomography, or PET scanning). Although all patients had symptoms on both sides of the body, the procedure was performed on only one side of the brain, enabling the untreated side to serve as a study control. The reported improvements were observed primarily on the treated side of the body beginning three months after the gene therapy procedure and persisted through the 12 months formal study period.

Neurologix sponsored the study as part of its ongoing efforts to develop this and other gene therapy approaches to the treatment of neurodegenerative and metabolic diseases. Principal investigators Michael G. Kaplitt, MD, PhD, and Matthew J. During, MD, PhD, performed the procedures at NewYork-Presbyterian Hospital/Weill Cornell Medical Center. Andrew Feigin, MD and David Eidelberg, MD of the Feinstein Institute for Medical Research, North Shore-Long Island Jewish Health System performed the clinical evaluations and the PET

scans. Neurologix scientists were also co-investigators in the study.

“This ground-breaking study represents not only an encouraging first step in the development of a promising new approach to Parkinson’s disease therapy, but also provides a platform to translate a variety of new gene therapy agents into human clinical trials for many devastating brain disorders,” said Paul Greengard, PhD, chairman of the Neurologix Scientific Advisory Board and recipient of the 2000 Nobel Prize for Physiology or Medicine for his work related to how brain cells communicate. “The significant and sustained improvements in clinical symptoms following treatment of only one side of the brain are impressive. Moreover, the PET results offer an important window into the function of the living brain in these patients, which supports a normalization of brain activity specific to the treated hemisphere.”

The study used an adeno-associated virus (AAV) vector to deliver an inhibitory gene (glutamic acid decarboxylase or “GAD”) to the subthalmic nucleus (STN) of the brain. In Parkinson’s disease, STN activity is abnormally increased, largely due to a deficit in GABA (gamma-aminobutyric acid), the major inhibitory neurotransmitter in the brain. Increasing GAD causes more GABA to be synthesized, thus helping to calm the STN over-activity. The value of this strategy has been demonstrated in previous human studies where reducing STN activity by either electrical stimulation or lesioning can help ameliorate the symptoms of advanced Parkinson’s disease.

The Phase 1 study was not specifically designed to assess efficacy. Nonetheless, the researchers reported the clinical outcomes to be very encouraging, with treated patients showing significant improvement in both the “on” and “off” states of their illness (the time periods in which they achieve or do not realize benefit from drug therapy) beginning at three months following surgery and continuing through the end of the study. These improvements occurred predominantly on the side of the

body corresponding to the side of the brain receiving treatment. Moreover, the absence of change at the earliest time point following treatment suggests that the improvement was not likely due to the surgical lesioning of the targeted brain region, as surgical approaches typically give rise to immediate, short-lasting benefit around the time of surgery, while prior studies of AAV-mediated gene therapy show that gene expression gradually increases to a maximal level over a period of weeks.

“We are very encouraged by the results of this trial and its publication in such a prestigious journal,” said John Mordock, Neurologix President and Chief Executive Officer. “Since the inception of the company, we have been a leader in developing gene therapy for neurological disease, and we feel that rigorous peer-review and publication of the results from this first-ever trial is an important milestone for this entire field. These promising observations certainly warrant further, more definitive testing of Neurologix’s technology, and we anticipate beginning a larger Phase 2 study in Parkinson’s disease later this year. Moreover, the results also provide a solid foundation for the development of our other therapeutic programs, including epilepsy where we plan to initiate a Phase 1 gene therapy study this year.”

Study Design

The study included 12 patients with advanced Parkinson’s disease, with four patients in each of three dose-escalating cohorts. All procedures were performed under local anesthesia and all 12 patients were discharged from the hospital within 48 hours of the procedure. At one year, all 12 patients as a group demonstrated a clinical improvement of 25% in the Unified Parkinson’s disease Rating Scale (UPDRS) compared to baseline (p