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NIH clinical trial begins for treatment of rare, fatal neurological disorder

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A clinical trial to evaluate a drug candidate called cyclodextrin as a possible treatment for Niemann-Pick disease type C1 (NPC), a rare and fatal genetic disease, will start today, researchers announced. Scientists from the NIH's National Center for Advancing Translational Sciences (NCATS) and the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) will conduct the clinical trial at the NIH Clinical Center. Reaching this trial stage required collaboration among government, industry, patient advocacy groups and academic researchers.

No therapies approved by the U.S Food and Drug Administration are available to treat NPC. The disease is characterized by the inability of cells to metabolize and dispose of cholesterol and lipids. It causes excessive amounts of cholesterol to accumulate within the liver, spleen and brain. NPC leads to progressive impairment of motor and intellectual function in early childhood. In childhood onset cases, life expectancy does not normally exceed a patient's teenage years.

"A crucial part of the NCATS mission is to collaborate within and beyond the NIH on projects to improve and accelerate the translational research process and deliver tangible improvements in human health," said NCATS Director Christopher P. Austin, M.D. "The cyclodextrin project is an important step in the development of both a potential treatment for a devastating disease that ravages the bodies and minds of its victims and a more efficient way to do translational projects."

In 2009, the NIH Therapeutics for Rare and Neglected Diseases (TRND) program, which is now led by NCATS, selected NPC cyclodextrin as one of its initial pilot projects to repurpose cyclodextrin from its conventional use as an ingredient in other drugs to a therapeutic for this rare disorder. TRND researchers work with project collaborators to conduct preclinical studies advancing potential treatments for rare and neglected diseases to human clinical trials.

TRND supported animal toxicology studies to evaluate the safety of cyclodextrin and all necessary regulatory efforts and also supported the development of an NPC biomarker. The biomarker test detects in the blood a modified cholesterol molecule specific to neuronal cells in the brain that would increase as a result of treatment with cyclodextrin.

TRND researchers and collaborators submitted the data in an Investigational New Drug application, filed Nov. 14, 2012, that the Food and Drug Administration (FDA) has now agreed is sufficient to start a Phase I clinical trial.

"The multidisciplinary nature of this collaboration establishes a generalizable model that can be used in the pursuit of treatment candidates for rare and neglected diseases," said John McKew, Ph.D., acting director of the NCATS Division of Pre-Clinical Innovation, chief of the Therapeutic Development Branch and director of TRND. "In addition, the FDA was instrumental in helping our team move this project into human clinical trials."

The NPC Phase I clinical trial will test multiple doses of cyclodextrin in nine patients. Forbes Porter, M.D., Ph.D., senior investigator and NICHD clinical director, and Nuria Carrillo, M.D., TRND staff physician, will conduct the trial. Dr. Porter also is conducting a natural history study of NPC to collect health information from patients to understand how the disease develops. The natural history study is critical

to understanding the clinical significance of a treatment for NPC patients.

"Initiation of this clinical trial is the culmination of two decades of basic and clinical research to understand and develop therapies for NPC," said Porter. "The efforts of the collaborators who make up the TRND NPC team have greatly accelerated translating cyclodextrin from the laboratory to the clinic."

The goal of the Phase I clinical trial is to determine a safe dose of cyclodextrin that will support an expanded Phase II trial to begin to evaluate the effectiveness of the drug. The team already is in the initial stages of collaborating with the Network for Excellence in Neuroscience Clinical Trials (NeuroNEXT), which is administered by the NIH's National Institute of Neurological Disorders and Stroke, to plan a Phase II multicenter trial.

The NPC cyclodextrin project was made possible by a collaborative approach that also included—in addition to NCATS, NICHD, National Institute of Neurological Disorders and Stroke (NINDS) and the FDA—the NIH's National Human Genome Research Institute; Johnson and Johnson Pharmaceutical Research & Development; Washington University in St. Louis School of Medicine; Albert Einstein School of Medicine, New York City, and University of Pennsylvania, Philadelphia. A number of family support groups have made significant contributions as well that have led to the launch of the clinical trial through the funding of NPC research and patient support. They include the Ara Parshegian Medical Research Foundation, the International Niemann Pick Disease Alliance, the National Niemann Pick Disease Foundation, and Support Of Accelerated Research for Niemann –Pick Type C.

The NPC clinical trial is the fourth TRND project to advance to human clinical trials in the last 15 months. The three other clinical trials are

evaluating treatments for sickle cell disease, chronic lymphocytic leukemia and hereditary inclusion body myopathy. TRND has a portfolio of 14 projects, which focus on rare and neglected tropical diseases.

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