Orchard Therapeutics Announces First Patient Randomized in Registrational Trial of OTL-203 for MPS-I Hurler Syndrome

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Gene therapy being developed as a one-time treatment to address the underlying cause of the disease by inserting a functional copy of the human IDUA gene into a patient's own hematopoietic stem cells

HURCULES study to enroll 40 patients at clinical sites across the U.S. and Europe

TOKYO, LONDON and BOSTON, Feb. 05, 2024 (GLOBE NEWSWIRE) -- Orchard Therapeutics, recently acquired by Kyowa Kirin with the goal of accelerating the delivery of new gene therapies to patients around the globe, today announced the first patient has been randomized at the M Health Fairview Masonic Children's Hospital in a registrational trial evaluating the efficacy and safety of OTL-203, an investigational hematopoietic stem cell (HSC) gene therapy, in patients with the Hurler subtype of mucopolysaccharidosis type I (MPS-IH). The trial, referred to as HURCULES, compares treatment with OTL-203 to standard of care with allogeneic hematopoietic stem cell transplant (HSCT), and is expected to enroll 40 MPS-IH patients at sites across the U.S. and Europe.

MPS-I is a rare, inherited neurometabolic disease caused by a deficiency of the alpha-L-iduronidase (IDUA) lysosomal enzyme resulting in the accumulation of glycosaminoglycans (GAGs) in multiple organs, including the musculoskeletal and central nervous systems, as well as the heart, eyes, and ears. It is estimated to occur globally in 1 in 100,000 live births. Approximately 60 percent of children born with MPS-I have the most severe subtype, MPS-IH, also called Hurler syndrome, and rarely live past the age of 10 when untreated. Current treatment options for MPS-IH include allogeneic hematopoietic stem cell transplant (HSCT) and enzyme replacement therapy (ERT), both of which have significant limitations.

"This is a substantial milestone in the development of OTL-203 as we work toward bringing an important new treatment option to children with MPS-IH and their families," said Leslie Meltzer, Ph.D., chief medical officer of Orchard Therapeutics. "Previously reported results from an earlier proof-of-concept study in patients showed robust metabolic correction, continued cognitive, motor, and physical development, as well as early improvements in skeletal, ocular and auditory health demonstrating that one-time treatment with OTL-203 has the potential to positively impact a broad range of clinical manifestations not fully addressed by the current standard of care."

In an earlier single-center proof-of-concept (PoC) study, eight patients diagnosed with MPS-IH were treated at Ospedale San Raffaele in Milan, Italy with investigational OTL-203 between July 2018 and December 2019. Throughout the follow-up period, a total of 26 serious adverse events (SAEs) were observed. The events were related to known complications of MPS-IH already present prior to treatment, protocol procedures or general illnesses of childhood, and all have resolved. One patient experienced an acute hypersensitivity reaction that was considered probably related to HSC gene therapy.

OTL-203 has received Fast Track and Rare Pediatric Disease (RPD) designations from the U.S. Food and Drug Administration (FDA), as well as priority medicines (PRIME) status from the European Medicines Agency (EMA). The program was originated by, and initially developed in partnership with, the San Raffaele Telethon Institute for Gene Therapy (SR-TIGET) in Milan, Italy.

"The complications associated with MPS-IH have a detrimental impact on patients' quality of life, and while transplantation may help improve outcomes, it is associated with significant morbidity and mortality," said Paul Orchard, M.D., a study investigator and professor in the Division of Pediatric Blood and Marrow Transplantation and Cellular Therapy Program at the University of Minnesota Medical School. "New options are needed to better address some of the more severe symptoms of the disease, such as neurocognitive function, growth and other skeletal issues. We look forward to working with the team at Orchard Therapeutics and other clinical sites around the world to facilitate enrollment in this study and characterize the potential clinical impact of OTL-203 on MPS-IH."

Currently, the University of Minnesota is actively recruiting patients with additional trial sites expected to begin recruitment in the coming months.

Summary of Previous OTL-203 Clinical Results

Interim results from the earlier PoC study published in *The New England Journal of Medicine* showed all patients had supraphysiological IDUA enzyme activity with an associated sustained decrease in GAG levels and stable cognitive performance post-treatment. In addition, all participants had progressed along expected growth percentiles of healthy children and exhibited longitudinal growth that was considered within the normal range adjusted for age and gender. In subsequent follow-up, study investigators have observed progressive acquisition of fine and gross motor skills, as well as evidence of continued growth within normal range and improvements in skeletal health with a median follow-up of 3.78 years (range: 3.14 to 4.58 years) as of May 2023.

In addition, Dr. Maria Ester Bernardo, clinical coordinator, pediatric clinical research unit at SR-TIGET and the principal investigator of the PoC study, detailed the first findings on other treatment outcomes, including ocular (eye) symptoms and auditory (hearing) function at the European Society of Cell and Gene Therapy (ESGCT) 30th Annual Congress. The presentation outlined favorable results for disease manifestations not fully addressed by the current standard of care and further highlights the potential of genetically repaired HSCs to migrate into and correct abnormalities in multiple tissues and organs.

Throughout the PoC study, treatment with OTL-203 has been generally well-tolerated with a safety profile consistent with the selected conditioning regimen. The viral vector integration profile was comparable with other Orchard Therapeutics lentiviral-based HSC gene therapy studies, and all participants had a stable and highly polyclonal repertoire. As part of the study, ERT was discontinued at least three weeks prior to any patient receiving

gene therapy, and none of those patients needed to re-start ERT post-treatment. Patients who entered the study with anti-IDUA antibodies present because of prior ERT treatment were no longer antibody positive within two months of treatment with OTL-203.

About the HURCULES Study
HURCULES—a study name that combines the target indication HURler syndrome and HerCULES, the classical mythological character—is a multi-center, randomized, active controlled clinical trial designed to evaluate the efficacy and safety of OTL-203 in patients with MPS-IH compared to standard of care with allogeneic HSCT. A total of 40 patients with a confirmed diagnosis of MPS-IH who meet the study inclusion criteria are being randomized 1:1 to receive either OTL-203 or allogeneic HSCT. The study is powered to demonstrate superiority of OTL-203 over allogeneic HSCT.

The primary endpoint, which will be measured at two years post-treatment, comprises a composite of clinically meaningful outcomes, including death, the need for rescue transplant, treatment failure, immunological complications, as well as severe cognitive and/or growth impairment. Secondary endpoints include biochemical markers, additional clinical assessments, as well as safety and tolerability. The company expects to activate six sites in the United States and Europe.

For more information, please visit www.clinicaltrials.gov (NCT06149403).

About MPS-I
Mucopolysaccharidosis type I (MPS-I) is a rare, inherited neurometabolic disease caused by a deficiency of the alpha-L-iduronidase (IDUA) lysosomal enzyme, which is required to break down sugar molecules called glycosaminoglycans (GAGs). The accumulation of GAGs across multiple organ systems results in multiple symptomatic manifestations of the disease including severe neurocognitive impairment, skeletal deformities, cardiovascular and pulmonary complications, impaired motor function, loss of hearing and corneal clouding. MPS-I occurs at an overall estimated frequency of one in every 100,000 live births. There are three subtypes of MPS-I. Approximately 60 percent of children born with MPS-I have the most severe subtype, called Hurler syndrome (MPS-IH), and rarely live past the age of 10 when untreated.

Treatment options for MPS-I include hematopoietic stem cell transplant and enzyme replacement therapy, both of which have limitations, such as inadequate impact on some of the more severe manifestations of disease, as well as significant morbidity and mortality. At present, Newborn Screening (NBS) for MPS-I has been established in multiple geographies, including the United States and Europe.

About OTL-203
OTL-203 is an investigational hematopoietic stem cell gene therapy being developed for the treatment of MPS-IH. It uses a modified virus to insert a functional copy of the human *IDUA* gene into a patient's cells. OTL-203 was originated by, and initially developed in partnership with, the San Raffaele Telethon Institute for Gene Therapy in Milan, Italy. OTL-203 has received Rare Pediatric Disease (RPD) and Fast Track designations from the U.S. FDA, as well as priority medicines (PRIME) status from the EMA.

About Orchard Therapeutics
Orchard Therapeutics, a Kyowa Kirin company, is a global gene therapy leader focused on ending the devastation caused by genetic and other severe diseases by discovering, developing, and commercializing new treatments that tap into the curative potential of hematopoietic stem cell (HSC) gene therapy. In this approach, a patient's own blood stem cells are genetically modified outside of the body and then reinserted, with the goal of correcting the underlying cause of disease with a single treatment.

Founded in 2015, Orchard's roots go back to some of the first research and clinical developments involving HSC gene therapy. Our team has played a central role in the evolution of this technology from a promising scientific idea to a potentially life-transforming reality. Today, as a vital part of Kyowa Kirin's global business, Orchard continuing to advance a pipeline of HSC gene therapies designed to address serious diseases where the burden is immense for patients, families and society and current treatment options are limited or do not exist.

For more information, please visit www.orchard-tx.com.

About Kyowa Kirin
Kyowa Kirin aims to discover novel medicines with life-changing value. As a Japan-based Global Specialty Pharmaceutical Company, we have invested in drug discovery and biotechnology innovation for more than 70 years and are currently working to engineer the next generation of antibodies and cell and gene therapies with the potential to help patients affected by a severe or rare disease. A shared commitment to our values, to sustainable growth, and to making people smile unites us across our four regions – Japan, Asia Pacific, North America, and EMEA/International. You can learn more about the business of Kyowa Kirin at: https://www.kyowakirin.com.

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