Orchard Therapeutics Announces U.S. FDA Clearance of IND Application for OTL-203 in MPS-IH

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Global registrational trial expected to commence in the second half of 2023

BOSTON and LONDON, Jan. 05, 2023 (GLOBE NEWSWIRE) -- Orchard Therapeutics (Nasdaq: ORTX), a global gene therapy leader, today announced the U.S. Food and Drug Administration (FDA) has cleared its Investigational New Drug (IND) application for OTL-203, a hematopoietic stem cell (HSC) gene therapy being developed for the treatment of the Hurler subtype of mucopolysaccharidosis type I (MPS-IH). The company expects to initiate a global registrational trial evaluating the efficacy and safety of OTL-203 compared to standard of care in the second half of 2023.

“Based on data from the proof-of-concept trial, treatment with a single administration of OTL-203 has the potential to address a range of multisystemic manifestations of MPS-IH,” said Leslie Meltzer, Ph.D., chief medical officer of Orchard Therapeutics. “Our recent interactions with the FDA have been productive and we look forward to advancing this registrational study designed to generate the data necessary to enable global regulatory submissions and potentially provide an urgently needed new treatment option for the MPS-IH community.”

The study 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 hematopoietic stem cell transplant (HSCT). A total of 40 patients with a confirmed diagnosis of MPS-IH who meet the study inclusion criteria will be randomized 1:1 to receive either OTL-203 or allogeneic HSCT. The study is powered to demonstrate superiority of OTL-203 over 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 treatment, treatment failure, immunological complications, as well as severe cognitive and growth impairment. Secondary endpoints include biochemical markers, additional clinical assessments, as well as safety and tolerability. The company expects to open up to six sites in the United States and Europe.

“The complications associated with MPS-IH involve multiple organ systems and have a lasting impact on patients’ quality of life despite treatment with allogeneic HSCT,” 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. “Existing therapeutic options are associated with significant morbidity and mortality. There is experience acquired over decades that treatment with allogeneic HSCT does not adequately impact manifestations of the disorder such as growth and other skeletal issues. Furthermore, patients can still experience an irreversible decline in neurocognitive function. We look forward to facilitating this study to characterize the potential clinical impact of OTL-203 for MPS-IH patients.”

In an earlier, single center proof-of-concept study, eight patients diagnosed with MPS-IH were treated with investigational OTL-203 between July 2018 and December 2019. Previously published results showed all patients had stable cognitive development post-treatment. In addition, at last follow-up (ranging from 12-24 months), 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. Treatment with OTL-203 was generally well-tolerated with no indication of insertional oncogenesis and no evidence of clonal dominance due to integration into oncogenes reported to date.

“MPS-IH is a devastating disease that places a significant burden on affected children and their families,” said Terri Klein, president and chief executive officer of the National MPS Society. “New treatment options are desperately needed to better address some of the more severe symptoms of the disease. We are encouraged by today's announcement and the hope that a one-time gene therapy could offer this community if approved.”

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 chronic 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 *IDUA* gene into a patient’s cells. OTL-203 is being developed in partnership with the San Raffaele Telethon Institute for Gene

Therapy in Milan, Italy. OTL-203 has received rare pediatric disease and priority medicines (PRIME) designations from the FDA and European Medicines Agency, respectively.

About Orchard Therapeutics
At Orchard Therapeutics, our vision is to end the devastation caused by genetic and other severe diseases. We aim to do this 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 in a single treatment.

In 2018, the company acquired GSK's rare disease gene therapy portfolio, which originated from a pioneering collaboration between GSK and the San Raffaele Telethon Institute for Gene Therapy in Milan, Italy. Today, Orchard is advancing a pipeline spanning pre-clinical, clinical and commercial stage 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.

Orchard has its global headquarters in London and U.S. headquarters in Boston. For more information, please visit www.orchard-tx.com, and follow us on Twitter and LinkedIn.

Availability of Other Information About Orchard
Investors and others should note that Orchard communicates with its investors and the public using the company website (www.orchard-tx.com), the investor relations website (ir.orchard-tx.com), and on social media (Twitter and LinkedIn), including but not limited to investor presentations and investor fact sheets, U.S. Securities and Exchange Commission filings, press releases, public conference calls and webcasts. The information that Orchard posts on these channels and websites could be deemed to be material information. As a result, Orchard encourages investors, the media, and others interested in Orchard to review the information that is posted on these channels, including the investor relations website, on a regular basis. This list of channels may be updated from time to time on Orchard's investor relations website and may include additional social media channels. The contents of Orchard's website or these channels, or any other website that may be accessed from its website or these channels, shall not be deemed incorporated by reference in any filing under the Securities Act of 1933.

Forward-looking Statements
This press release contains forward-looking statements, which are made pursuant to the safe harbor provisions of the Private Securities Litigation Reform Act of 1995. All statements that are not statements of historical facts are, or may be deemed to be, forward-looking statements. Forward-looking statements include express or implied statements relating to, among other things, Orchard's business and product development strategy and goals, including the therapeutic potential of OTL-203, Orchard's expectations with respect to regulatory submissions for its product candidates, including OTL-203, and Orchard's expectations regarding its ongoing preclinical and clinical trials, including the timing of enrollment for clinical trials and release of additional preclinical and clinical data, and the likelihood that data from clinical trials will be positive and support further clinical development and regulatory approval of Orchard's product candidates. These statements are neither promises nor guarantees and are subject to a variety of risks and uncertainties, many of which are beyond Orchard's control, which could cause actual results to differ materially from those contemplated in these forward-looking statements. In particular, these risks and uncertainties include, without limitation: the risk that prior results, such as signals of safety, activity or durability of effect, observed from clinical trials of OTL-203 will not continue or be repeated in Orchard's ongoing or planned clinical trials of OTL-203, will be insufficient to support regulatory submissions or support or maintain marketing approval in the US or European Union, or that long-term adverse safety findings may be discovered; and the risk that any one or more of Orchard's product candidates, including the OTL-203, will not be approved, successfully developed or commercialized. Given these uncertainties, the reader is advised not to place any undue reliance on such forward-looking statements.

Other risks and uncertainties faced by Orchard include those identified under the heading "Risk Factors" in Orchard's most recent annual or quarterly report filed with the U.S. Securities and Exchange Commission (SEC), as well as subsequent filings and reports filed with the SEC. The forward-looking statements contained in this press release reflect Orchard's views as of the date hereof, and Orchard does not assume and specifically disclaims any obligation to publicly update or revise any forward-looking statements, whether as a result of new information, future events or otherwise, except as may be required by law.

Dr. Paul Orchard is a paid consultant for Orchard Therapeutics.

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