Orchard Therapeutics Announces Presentation of Additional Positive Data from Proof-of-concept Study of OTL-203 in MPS-IH at ESGCT 2023

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New clinical data beyond previously reported neurological and skeletal results demonstrate favorable outcomes for multiple disease manifestations not effectively addressed by the current standard of care

BOSTON and LONDON, Oct. 26, 2023 (GLOBE NEWSWIRE) -- Orchard Therapeutics (Nasdaq: ORTX), a global gene therapy leader, today announced a range of interim clinical outcomes, in addition to the previously reported neurological and skeletal results, from the company's ongoing proof-of-concept (PoC) study of OTL-203, a hematopoietic stem cell (HSC) gene therapy in development for the treatment of the Hurler subtype of mucopolysaccharidosis type I (MPS-IH). The data were presented at the European Society of Gene and Cell Therapy (ESGCT) 30th Annual Congress taking place October 24-27, 2023, in Brussels.

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 eyes, ears, heart, as well as the musculoskeletal and central nervous systems. It is estimated to occur globally in approximately 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 chronic enzyme replacement therapy (ERT), neither of which effectively address the broad range of clinical manifestations of the disease.

"These positive data presented at ESGCT add to the growing body of evidence underscoring the potential of a one-time HSC gene therapy to correct a range of disease manifestations not effectively addressed by the current standard of care," said Leslie Meltzer, Ph.D., chief medical officer of Orchard Therapeutics. "The complications associated with MPS-IH involve multiple organ systems and have an adverse impact on patients' quality of life. We continue to be encouraged by these results from our proof-of-concept study and look forward to initiating our global registrational trial later this year."

In the single-center 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. Interim results published in *The New England Journal of Medicine* showed all patients had 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.

Additional Ocular and Auditory Clinical Data Presented at ESGCT 2023

At ESGCT, Dr. Maria Ester Bernardo, clinical coordinator, pediatric clinical research unit at San Raffaele Telethon-Institute for Gene Therapy (SR-TIGET) and the principal investigator of the PoC study, detailed the first findings on other treatment outcomes, including ocular (eye), and auditory (hearing) function. Results showed:

- Treatment with OTL-203 resulted in improvement (62.5% of patients; n=5/8) or stabilization (37.5% of patients; n=3/8) of corneal clouding at the time of last follow-up (ranging from 3.14-4.58 years) compared to baseline measured prior to administration with OTL-203.
    - Importantly, following treatment with OTL-203, no patients reported photophobia (light sensitivity), or any other ophthalmological symptoms typically associated with MPS-IH.
- At last follow-up, 50.0% of patients (n=4/8) showed normal hearing function, and none developed severe hearing loss. In addition, no treated patients have required a hearing aid or any intervention for hearing loss following administration with OTL-203 as of last follow-up.
- Follow-up to fully assess and characterize the potential impact of HSC gene therapy on ocular and auditory manifestations of MPS-IH is ongoing.

Summary of Previously Reported Safety Results

Treatment with OTL-203 has been generally well-tolerated with a safety profile consistent with the selected conditioning regimen. Anti-alpha-L-iduronidase (IDUA) antibodies present prior to gene therapy as a result of ERT were not seen in any patient within two months following treatment. In addition, ERT was discontinued at least three weeks prior to any patient receiving gene therapy treatment, and no patients have re-started ERT post-treatment. The lentiviral vector integration profile was consistent with other lentiviral-based HSC gene therapy studies, and all participants had a stable and highly polyclonal repertoire.

Global Registrational Trial Expected to Commence by Year-end

Following the promising results observed in the proof-of-concept study, Orchard Therapeutics is initiating 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 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 activate up to six sites in the United States and Europe, the first of which is planned to open enrollment later this year.

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 X (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 (X: 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, the therapeutic potential of Orchard's products and 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 products will not be successfully commercialized, and the risk that long-term adverse safety findings may be discovered. 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.

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