Orchard Therapeutics Announces New England Journal of Medicine Publication of Interim Proof-of-concept Study Results of OTL-203 for Hurler Syndrome

November 18, 2021

100 percent overall survival with median follow-up of two years post-treatment with HSC gene therapy

Preliminary findings show promising metabolic and early clinical outcomes

Results warrant further evaluation in global registrational study expected to be initiated in 2022 following recent meeting to discuss trial design with U.S. and European regulators

BOSTON and LONDON, Nov. 18, 2021 (GLOBE NEWSWIRE) -- Orchard Therapeutics (Nasdaq: ORTX), a global gene therapy leader, today announced data published in the *New England Journal of Medicine (NEJM)* evaluating the safety and efficacy of OTL-203 for the treatment of the Hurler subtype of Mucopolysaccharidosis type I (MPS-IH). OTL-203 is an investigational autologous hematopoietic stem cell (HSC) gene therapy comprising an individual's own CD34 $^{+}$ HSCs transduced *ex vivo* with a lentiviral vector encoding the *alpha-L-iduronidase* (*IDUA*) gene.

Mucopolysaccharidosis type I (MPS-I) is a rare, inherited neurometabolic disease caused by a deficiency of the alpha-L-iduronidase (IDUA) lysosomal enzyme. 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.

"MPS-IH places an enormous burden on affected children, their families and society," said Maria Ester Bernardo, Ph.D. head of the pediatric bone marrow transplantation unit at San Raffaele Hospital in Milan and a senior author of the *NEJM* manuscript. "Current treatment options are associated with significant limitations and do not adequately address some of the more severe manifestations of disease. Based on these preliminary first-in-human data, administration of a one-time HSC gene therapy designed to overexpress IDUA represents a potential step forward in the treatment landscape."

In this ongoing non-randomized, single center proof-of-concept study, eight patients diagnosed with MPS-IH were treated with OTL-203 between July 2018 and December 2019. The primary endpoints included blood IDUA activity (up to supraphysiologic levels) at one-year post-treatment, overall survival, hematological engraftment by day 45, as well as short-and long-term safety monitoring. Secondary endpoints included assessment of anti-IDUA antibody immune response, normalization of urinary glycosaminoglycans (GAGs) and growth velocity at one-, three-, and five- years post-treatment, among other exploratory endpoints.

"Whilst the data observed in children treated with OTL-203 are preliminary, we are encouraged by the stable cognitive and motor function as well as growth—all of which are in line with normal patterns," said Bobby Gaspar, M.D., Ph.D., chief executive officer of Orchard Therapeutics. "Following our previously announced parallel scientific advice meeting with U.S. and European regulators, we look forward to further evaluating the potentially transformative impact OTL-203 may have on the most devastating effects of MPS-I in a global Phase 3 registrational trial that we plan to commence in 2022."

Summary of Results Published in *The New England Journal of Medicine*

All participants showed prompt and sustained engraftment of gene-corrected HSCs and achieved supraphysiologic blood IDUA activity by one-month post-treatment. At the time of analyses, results showed:

Efficacy Results

- At 12 months, all eight participants (100 percent) achieved the primary endpoint of supraphysiologic blood IDUA activity, (median: 107.95 µmol/L/h; range: 30-138.6), above the 97.5 percentile (24.8 µmol/L/h) of age-matched healthy children. By last available follow-up (12 to 24 months), IDUA activity was above the upper limit of normal and supraphysiological in all eight participants. This was associated with a decrease in urinary glycosaminoglycans (GAG) levels to normal or near normal levels by three to six months in all participants, remaining stable up to last available follow-up. Previously undetectable levels of IDUA in cerebrospinal fluid at baseline became evident in all participants post-treatment, starting from the first follow up at three months and persisting up to the latest available follow-up (median: 0.5 µmol/L/h; range: 0.12-4.78). This corresponded with a rapid decline in GAG levels in the cerebrospinal fluid suggesting a profound metabolic correction within the central nervous system.
- All eight participants showed stable cognitive development post-treatment and continued to progressively acquire motor

skills over time, as shown by the stability of Gross and Fine Motor Quotient Scores at time of last follow up of 12 to 24 months.
- At last follow-up (ranging from 12 to 24 months), all participants continue progress along expected growth percentiles of healthy children and exhibited longitudinal growth that was considered within the normal range adjusted for age and gender.
- Range of motion assessments at last available follow-up (six to 24 months) showed improvements in joint range of motion compared to pre-treatment as measured by goniometry in shoulder flexion, shoulder abduction, and knee extension angles.
- *In vivo* gene marking with OTL-203 stabilized after six months, reaching a median vector copy number (VCN) of 0.98 per genome (range: 0.17-3.95) in peripheral blood mononuclear cells at nine to 12 months post-treatment.

Safety Results

- Overall survival was 100 percent through the end of available follow-up.
- Anti-IDUA IgG antibodies detected at baseline (pre-treatment) in five of seven participants who were taking enzyme replacement therapy prior to treatment with OTL-203 were no longer detectable within the first three months following OTL-203 administration. Enzyme replacement therapy was stopped at least three weeks before OTL-203 and not restarted in any patient.
- Throughout the follow up period, 19 serious adverse events (SAEs) were observed, seven of which were related to known complications of MPS-IH and were already present prior to treatment, and all have resolved.
- No participants developed graft-versus-host-disease, as expected given the autologous nature of OTL-203.
- 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.

About OTL-203 and 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 (also known as 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. Though early intervention with enzyme replacement therapy has been shown to delay or prevent some clinical features of the condition, it has only limited efficacy on neurological symptoms. OTL-203 is an investigational *ex vivo* autologous hematopoietic stem cell gene therapy being studied for the treatment of MPS-I. Orchard was granted an exclusive worldwide license to intellectual property rights to research, develop, manufacture and commercialize the gene therapy program for the treatment of MPS-I developed by the San Raffaele Telethon Institute for Gene Therapy in Milan, Italy.

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 has a deep 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 and these channels, and 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 certain forward-looking statements about Orchard's strategy, future plans and prospects, which are made pursuant to the safe harbor provisions of the Private Securities Litigation Reform Act of 1995. Such forward-looking statements may be identified by words such as "plans," "anticipates," "believes," "expects," "intends," "projects," and "future" or similar expressions that are intended to identify forward-looking statements. Forward-looking statements include express or implied statements relating to, among other things, Orchard's business strategy and goals, including with respect to its plans and expectations for the development of its product candidates, including the product candidates referred to in this release, and the therapeutic and commercial potential of its 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 any one or

more of Orchard's product candidates, including the product candidates referred to in this release, will not be approved, successfully developed or commercialized; the risk that prior results, such as signals of safety, activity or durability of effect, observed from preclinical studies or clinical trials of Orchard's product candidates will not be repeated or continue in ongoing or future studies or trials involving its product candidates; the risk that the market opportunity for its product candidates may be lower than estimated; and the severity of the impact of the COVID-19 pandemic on Orchard's business, including on preclinical and clinical development, its supply chain and commercial programs. 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 quarterly report on Form 10-Q for the quarter ended September 30, 2021, as 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.

Contacts

Investors
Renee Leck
Director, Investor Relations
+1 862-242-0764
Renee.Leck@orchard-tx.com

Media
Benjamin Navon
Director, Corporate Communications
+1 857-248-9454
Benjamin.Navon@orchard-tx.com