Orchard Therapeutics Presents New Interim Data from OTL-203 Proof-of-concept Study for MPS-I

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First Primary Outcome Measure Met with All Eight Patients Achieving Hematologic Engraftment

Improved Motor Skills, Stable Cognitive Scores and Normal Growth Seen in First Two Patients

One-year Follow-up Results and Initiation of Registrational Trial Expected in 2021

BOSTON and LONDON, May 15, 2020 (GLOBE NEWSWIRE) -- Orchard Therapeutics (Nasdaq: ORTX), a global gene therapy leader, today announced new interim data from an ongoing proof-of-concept clinical trial evaluating the safety and efficacy of OTL-203, an *ex vivo* autologous hematopoietic stem cell (HSC) gene therapy in development for the treatment of mucopolysaccharidosis type I (MPS-I) at the San Raffaele Telethon Institute for Gene Therapy (SR-Tiget) in Milan, Italy. The results are being shared virtually in two presentations at the American Society of Gene & Cell Therapy (ASGCT) 23rd Annual Meeting, including the main dataset in an invited oral presentation today.

“We have made strong progress with the MPS-I clinical trial and are pleased to see these interim results, with all patients achieving hematological recovery in less than 45 days – a primary outcome measure – as well as supraphysiological levels of IDUA enzyme in the blood. In addition, the trial results to date have shown promising preliminary clinical effects on motor skills, IQ and growth in the first two patients with 12 and 18 months of follow-up,” said Maria Ester Bernardo, M.D., Ph.D., co-principal investigator at SR-Tiget. “We also observed reconstitution of enzyme activity in the cerebral spinal fluid (CSF) in the first two treated patients with 12 months of follow-up, complemented by a decrease in glycosaminoglycan levels in the CSF. We look forward to continuing to assess the outcomes of this investigational gene therapy for patients with this often-fatal condition.”

Interim Study Results
As of April 2020, all eight patients with the severe Hurler subtype of MPS-I have been treated with OTL-203. Patients have been followed for a minimum of three months, with the longest follow-up extending out to 18 months.

The primary outcome measures of the trial include overall survival, safety, hematological engraftment by day 45 following treatment and biological efficacy as measured by alpha-L-iduronidase (IDUA) lysosomal enzyme activity in the blood at one-year post-treatment. Treatment with OTL-203 and the selected conditioning regime were well-tolerated across all eight patients and demonstrated:

- Rapid hematologic reconstitution, with neutrophil and platelet engraftment within 21 days following treatment – achieving a primary outcome measure of hematological engraftment within 45 days of infusion.
- Biological efficacy demonstrated by supranormal IDUA enzyme expression in peripheral blood, with the first two patients treated achieving stable supranormal levels up to 12 months post gene therapy.

Key secondary and exploratory outcome measures include normalization of urinary glycosaminoglycans (GAGs), growth velocity and effects on motor and cognitive function at one- and two-years post-treatment. Treatment with OTL-203 demonstrated:

- In all eight patients, interim data showed high levels of metabolic correction with reduction in GAG levels in urine and cerebral spinal fluid (CSF).
- For the first two treated patients, with 18 and 12 months of follow-up, clinical data showed:
    - Rapid metabolic correction of GAG levels in the urine and CSF, reflecting restoration of IDUA enzyme expression in the periphery and in the central nervous system.
    - Improved motor function and acquisition of cognitive and language skills.
    - Continued growth progressing above the 50th percentile of normal.
    - Improved range of motion (an indicator of joint stiffness).
    - Improvement of brain and spine MRI scores.

“We are extremely encouraged by data emerging from the MPS-I program, where we are seeing correction of biochemical parameters as well as early clinical evidence of the potentially transformative effects of OTL-203,” said Bobby Gaspar, M.D., Ph.D., chief executive officer of Orchard. “These data further support the hypothesis that our hematopoietic stem cell gene therapy approach could have potential future applications to treat a range of genetic neurometabolic disorders. Given the historical difficulty in treating these types of conditions, we are committed to advancing our programs in this area as quickly as possible for patients in need and are excited by the opportunity to initiate the registrational trial for this program in 2021.”

The proof-of-concept study is ongoing and additional interim results are planned to be reported in the second half of 2020. The company also expects to release full proof-of-concept results and initiate the registrational study for OTL-203 in 2021.

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 symptoms including neurocognitive impairment, skeletal deformity, loss of vision and hearing, and cardiovascular and pulmonary complications. 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, 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 significant 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 *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
Orchard Therapeutics is a global gene therapy leader dedicated to transforming the lives of people affected by rare diseases through the development of innovative, potentially curative gene therapies. Our *ex vivo* autologous gene therapy approach harnesses the power of genetically modified blood stem cells and seeks to correct the underlying cause of disease in a single administration. In 2018, Orchard 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. Orchard now has one of the deepest and most advanced gene therapy product candidate pipelines in the industry spanning multiple therapeutic areas where the disease burden on children, families and caregivers is immense 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.com/orchard_tx and www.linkedin.com/company/orchard-therapeutics), 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 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. Forward-looking statements include express or implied statements relating to, among other things, Orchard's business strategy and goals, the therapeutic potential of Orchard's product candidates, including the product candidate or candidates referred to in this release, and Orchard's expectations regarding the timing of clinical trials and announcement of clinical data for 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 severity of the impact of the COVID-19 pandemic on Orchard's business, including on clinical development and commercial programs; the risk that any one or more of Orchard's product candidates, including the product candidate or candidates referred to in this release, will not be approved, successfully developed or commercialized; the risk of cessation or delay of any of Orchard's ongoing or planned clinical trials; the risk that Orchard may not successfully recruit or enroll a sufficient number of patients for its clinical trials; the risk that prior results, such as signals of safety, activity or durability of effect, observed from preclinical studies or clinical trials will not be replicated or will not continue in ongoing or future studies or trials involving Orchard's product candidates; the delay of any of Orchard's regulatory submissions; the failure to obtain marketing approval from the applicable regulatory authorities for any of Orchard's product candidates or the receipt of restricted marketing approvals; and the risk of delays in Orchard's ability to commercialize its product candidates, if approved. 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 annual report on Form 10-K for the year ended December 31, 2019, as filed with the U.S. Securities and Exchange Commission (SEC) on February 27, 2020, 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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