Orchard Therapeutics Announces Additional Interim Results from Proof-of-Concept Study of OTL-203 for MPS-I

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Data on all eight patients demonstrate sustained engraftment and supranormal IDUA enzyme expression

Translation of metabolic correction to clinical outcomes in first two patients continues to support potential of hematopoietic stem cell gene therapy in a second neurometabolic disorder

Data support planned initiation of registrational trial in 2021

BOSTON and LONDON, Sept. 01, 2020 (GLOBE NEWSWIRE) -- Orchard Therapeutics (Nasdaq: ORTX), a global gene therapy leader, today announced additional interim data from an ongoing proof-of-concept clinical trial evaluating the safety and efficacy of OTL-203, an investigational *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 readout from the primary endpoint at one year of follow-up is expected in 2021. Today's results are being shared virtually in an invited oral presentation at the 46th Annual Meeting of the European Society for Blood and Bone Marrow Transplantation (EBMT).

“We continue to see encouraging data from the ongoing clinical trial in MPS-I, including promising preliminary clinical effects on motor development, acquisition of cognitive skills and growth in the first two patients that were treated now 1.5 and 2 years ago, respectively. Additionally, new preliminary analyses of radiological outcome measures suggest that treatment with OTL-203 leads to stabilization or improvement in disease-related neurological abnormalities, as measured by brain and spine MRI, which we look to confirm with longer follow-up,” said Maria Ester Bernardo, M.D., Ph.D., principal investigator at SR-Tiget. "These data, taken together with those from clinical studies of HSC gene therapy for other metabolic disorders and leukodystrophies, support the potential for this therapeutic approach to correct a wide spectrum of multisystemic manifestations of the disease, bringing clinically meaningful benefits for patients.”

Interim Study Results

Eight patients with the severe Hurler subtype of MPS-I had been treated with OTL-203 in the ongoing proof-of-concept study, which completed enrollment in December 2019. As of July 2020, all patients had been followed for a minimum of six months, with the longest follow-up extending out to 24 months. Treatment with OTL-203 was generally well-tolerated with a safety profile consistent with the selected conditioning regimen. Consistent with previous analyses, treatment across all eight patients continued to demonstrate:

- Rapid hematologic reconstitution, with neutrophil and platelet engraftment within 21 days following treatment.
- Biological efficacy established by sustained supranormal alpha-L-iduronidase (IDUA) enzyme expression in peripheral blood for all patients within 3 months post-gene therapy and up to 18 months in the first treated patient.
- Metabolic correction as measured by reduction in glycosaminoglycan (GAG) levels in urine achieved in all patients by 6 months post-gene therapy, with sustained correction out to 18 months in the first treated patient.

- Further results for the first two treated patients demonstrated:
    - Rapid metabolic correction of GAG levels in the cerebral spinal fluid (CSF), reflecting restoration of IDUA enzyme expression in the central nervous system.
    - Improved motor function and acquisition of cognitive and language skills.
    - Stabilization or improvement in white matter abnormalities, cervical canal stenosis, kyphosis and vertebra deformity, as measured by brain and spine MRI scores.
    - Continued growth progression above the 50th percentile of normal.
    - Improved range of motion (an indicator of joint stiffness).

“We continue to see positive trends in all biomarker and clinical measures as we follow patients in the OTL-203 proof of concept study for longer periods of time,” said Bobby Gaspar, M.D., Ph.D., chief executive officer of Orchard. “With a growing amount of data to support advancing this program, we have recently convened a panel of disease experts to develop a design for a registrational trial that we intend to take to the regulators in advance of initiating the study in 2021 and ultimately progressing towards commercialization.”

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 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

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 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 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 "anticipates," "believes," "expects," "plans," "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, the therapeutic potential of Orchard's product candidates, including the product candidates referred to in this release, Orchard's expectations regarding the timing of clinical trials for its product candidates, including the product candidates referred to in this release, the timing of interactions with regulators and regulatory submissions related to ongoing and new clinical trials for its product candidates, the timing of announcement of clinical data for its product candidates, and the likelihood that such data will be positive and support further clinical development and regulatory approval of these 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, its supply chain and commercial programs; the risk that Orchard will not realize the anticipated benefits of its new strategic plan or the expected cash savings associated with such plan; the risk that any one or more of Orchard's product candidates, including the product candidates referred to in this release, will not be successfully developed, approved 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 or that long-term adverse safety findings may be discovered; 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 quarterly report on Form 10-Q for the quarter ended June 30, 2020, 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
Molly Cameron
Manager, Corporate Communications
+1 978-339-3378
media@orchard-tx.com

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