# Orchard Therapeutics Announces Interim Data for OTL-203 Showing Positive Clinical Results in Multiple Disease Manifestations of Mucopolysaccharidosis Type I Hurler Syndrome (MPS-IH)

February 9, 2021

*All eight patients treated with OTL-203 show stable cognitive function, motor function and growth within the normal range at multiple data points post-treatment*

*Supportive initial OTL-201 biomarker data for mucopolysaccharidosis type IIIA (MPS-IIIA or Sanfilippo syndrome type A) in three patients*

*Data in multiple posters highlight ongoing work in patient identification and access to treatment for metachromatic leukodystrophy (MLD)*

*IR webinar today at 4:30 p.m. ET with Dr. Simon Jones from Manchester Centre for Genomic Medicine to review OTL-203 and OTL-201 data*

BOSTON and LONDON, Feb. 09, 2021 (GLOBE NEWSWIRE) -- Orchard Therapeutics (Nasdaq: ORTX), a global gene therapy leader, today announced new data from several of its hematopoietic stem cell (HSC) gene therapies in development for neurodegenerative disorders, including interim data on multiple clinical outcomes for OTL-203 in MPS-I, encouraging preliminary biomarker data for OTL-201 in MPS-IIIA and natural history data in MLD supporting future patient identification and market access. Today's results are being shared virtually at the 17th Annual WORLD*Symposium.*

"We are thrilled to announce an extensive set of powerful presentations from our neurometabolic programs by investigators, partners and employees at this year's WORLD *Symposium*," said Bobby Gaspar, M.D., Ph.D., chief executive officer of Orchard. "With a growing body of clinical data demonstrating cognitive and motor function within the normal range in multiple conditions, the potential for HSC gene therapy to make a durable impact in devastating disorders of the central nervous system has never been so compelling. Beyond our development activities, we are executing a robust disease education, patient identification and market access strategy to support the European launch of Libmeldy™ in MLD and those of future gene therapies."

**OTL-203 for MPS-I Clinical Proof-of-Concept Results**

Patients with the Hurler subtype of MPS-I suffer from a range of symptoms including neurocognitive impairment and skeletal deformities that lead to impaired growth in the first decade of life. Also, patients often have compromised motor function that progresses with age and limited range of motion due to the accumulation of substrates known as glycosaminoglycans (GAGs) in the joints. Treatment options for MPS-IH include hematopoietic stem cell transplant and chronic enzyme replacement therapy (ERT), both of which have significant limitations.

Eight patients with MPS-IH have been treated with OTL-203 in the proof-of-concept study being conducted at the San Raffaele Telethon Institute for Gene Therapy (SR-Tiget) in Milan, Italy. As of November 2020, follow-up in all patients has reached at least 12 months. Orchard's request for parallel scientific advice from the U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA) has been accepted with the intention of seeking feedback in advance of initiating a registrational study for OTL-203 by year-end 2021.

As of November 2020, the interim data supporting clinical proof-of-concept illustrate the following:

- Safety: 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.

- Biomarker data: Treatment demonstrated rapid and sustained metabolic correction with all patients achieving supra-physiological IDUA expression in dried blood spot samples at 12 months (a primary efficacy endpoint). Associated with this, the results demonstrated increased IDUA expression in the cerebral spinal fluid (CSF), with reduction of GAGs in CSF and normalization of GAG levels in urine.

- New clinical results (n=8):
  - Stable cognitive performance, as evaluated by cognitive age-equivalence using the Bayley scale, was shown in all patients post-treatment, with follow-up ranging from 6 months to 2 years.
  - Longitudinal growth that was within age-appropriate reference ranges was seen in all patients post-treatment, with

follow-up ranging from 9 months to 2 years.
- Stable motor function was seen in all patients compared to pre-treatment, with follow-up ranging from 9 months to 1.5 years.
- Improved range of motion (less joint stiffness) was shown in all patients compared to pre-treatment, with follow-up ranging from 9 months to 1.5 years.

"For the majority of patients with MPS-I Hurler, existing therapeutic options such as enzyme replacement therapy and HSCT often fail to adequately address the disease's impact on cognition, motor skills and growth," said Bernhard Gentner, M.D., investigator at SR-Tiget. "With follow-up data showing stable cognitive performance and normal longitudinal growth in multiple patients treated with OTL-203, we are encouraged by the potential for HSC gene therapy to correct a wide spectrum of multisystemic manifestations of the disease and bring clinically meaningful benefit to patients."

**OTL-201 for MPS-IIIA Preliminary Proof-of-Concept Results**

MPS-IIIA, also known as Sanfilippo syndrome type A, is a rare and life-threatening neurometabolic disease with no approved treatments. Children with MPS-IIIA are born with a mutation in the *N-sulphoglucosamine sulphohydrolase* (*SGSH*) gene, which is involved in the breakdown of sugar molecules called mucopolysaccharides, including heparan sulfate. The buildup of mucopolysaccharides in the brain and other tissues leads to intellectual disability and loss of motor function.

As of February 2021, preliminary results from the first three patients treated with OTL-201 for MPS-IIIA are showing promising tolerability, engraftment and biomarker data over the initial three-month follow-up period.

- Safety: The treatment has been generally well-tolerated in the first three patients with no treatment-related serious adverse events (SAEs), and all transplant-related SAEs and adverse events have resolved.
- Engraftment: Data supported evidence of hematological engraftment, as illustrated by the rapid recovery of neutrophils, platelets and hemoglobin levels post myeloablative conditioning in all three patients within three months of treatment.
- Biomarker data:
    - SGSH enzyme expression in leukocytes and CD15+ cells increased from undetectable at baseline to supra-physiological levels at three months in all three patients treated.
    - Investigators reported a reduction of urinary GAG levels to within the normal range by three months in the first two patients treated with evaluable data.

A fourth patient has recently been enrolled in the study. Enrollment is expected to complete (n=5) this year and the company intends to release additional interim results later in 2021. The study, which is being sponsored by The University of Manchester (UoM), conducted at Royal Manchester Children's Hospital, part of Manchester University NHS Foundation Trust and funded by Orchard, follows over a decade of development and pre-clinical work by Brian Bigger, Ph.D., Professor of Cell and Gene Therapy at UoM.

**Company to Host IR Webinar Today (February 9, 2021) at 4:30 p.m. ET**

Orchard will be hosting a virtual investor webinar with members of management and Dr. Simon Jones, consultant in pediatric inherited metabolic diseases at the Willink Unit, Manchester Centre for Genomic Medicine at Saint Mary's Hospital today at 4:30 p.m. ET to review the OTL-203 and OTL-201 data presented at the WORLD*Symposium*. Registration and webcast information are available under "Events" in the Investors & Media section of the company's website at www.orchard-tx.com. A replay of the webcast will be archived following the event.

**MLD Patient Identification and Market Access**

Data supporting Orchard's multi-pronged MLD patient identification strategy were also presented at the WORLD *Symposium* via two e-posters focused on disease education and newborn screening. The first reported language and words commonly used by parents and other caregivers to describe initial disease symptoms, which could aid physicians in making an earlier diagnosis of MLD. A separate poster highlighted the progress toward demonstrating the reproducibility of a clinically validated assay as part of a prospective newborn screening study in northern Germany. The poster reports on the assay's set-up and initial validation on 1,700 newborns for MLD-related markers to date.

Data assessing the quality of life impact of MLD on patients and their caregivers were presented in the form of a caregiver burden survey and a first-in-kind study measuring health utility associated with both the motor and cognitive aspects of MLD. This health utility study evaluated the severity of MLD and also offered a comparison to published utility values measuring other devastating rare diseases. These data are an important component of the company's value assessment of Libmeldy.

Data describing the annual healthcare resource utilization (HCRU) associated with management of MLD patients through the United Kingdom National Health Service was also presented. Orchard intends to utilize this collective health economic research to support access discussions for eligible MLD patients in Europe and beyond.

Updated clinical data for OTL-200 in patients with MLD were also presented, including results in early-symptomatic early-juvenile (ES-EJ) patients as well as new data from a cryopreserved formulation of OTL-200. The cryopreserved formulation of OTL-200 was recently approved by the EMA as Libmeldy, for early-onset MLD patients, in December 2020.

**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 OTL-201 and MPS-IIIA**

Mucopolysaccharidosis type IIIA (MPS-IIIA, also known as Sanfilippo syndrome type A) is a rare and life-threatening metabolic disease. People with MPS-IIIA are born with a mutation in the *N-sulphoglucosamine sulphohydrolase* (*SGSH*) gene, which is involved in the breakdown of sugar molecules called mucopolysaccharides, including heparan sulfate. The buildup of mucopolysaccharides in the brain and other tissues leads to intellectual disability and loss of motor function. MPS-IIIA occurs approximately once in every 100,000 live births. Life expectancy of children born with MPS-IIIA is estimated to be between 10-25 years.[1] There are currently no approved treatment options for MPS-IIIA. OTL-201 is an investigational *ex vivo* autologous hematopoietic stem cell gene therapy being studied for the treatment of MPS-IIIA. It uses a modified virus to insert a functional copy of the *SGSH* gene into a patient's cells.

**About The University of Manchester**

The University of Manchester, a member of the prestigious Russell Group, is one of the UK's largest single-site universities with more than 40,000 students – including more than 10,000 from overseas. It is consistently ranked among the world's elite for graduate employability. The University is also one of the country's major research institutions, rated fifth in the UK in terms of 'research power' (REF 2014). World-class research is carried out across a diverse range of fields including cancer, advanced materials, global inequalities, energy and industrial biotechnology.

**About Manchester University NHS Foundation Trust**

Manchester University NHS Foundation Trust is one of the largest NHS trusts in England and a leading provider of specialist healthcare services. Its nine hospitals are home to hundreds of world class clinicians and academic staff committed to finding patients the best care and treatments. This includes Royal Manchester Children's Hospital (RMCH), one of the largest children's hospitals in the UK with an international reputation as a centre of excellence for research and innovation. More information is available at www.mft.nhs.uk.

**About Libmeldy™ / OTL-200**

Libmeldy (autologous $CD34^+$ cell enriched population that contains hematopoietic stem and progenitor cells (HSPC) transduced *ex vivo* using a lentiviral vector encoding the human *arylsulfatase-A* (*ARSA*) gene), also known as OTL-200, has been approved by the European Commission for the treatment of MLD in eligible early-onset patients characterized by biallelic mutations in the *ARSA* gene leading to a reduction of the ARSA enzymatic activity in children with i) late infantile or early juvenile forms, without clinical manifestations of the disease, or ii) the early juvenile form, with early clinical manifestations of the disease, who still have the ability to walk independently and before the onset of cognitive decline. Libmeldy is the first therapy approved for eligible patients with early-onset MLD.

The most common adverse reaction attributed to treatment with Libmeldy was the occurrence of anti-ARSA antibodies. In addition to the risks associated with the gene therapy, treatment with Libmeldy is preceded by other medical interventions, namely bone marrow harvest or peripheral blood mobilization and apheresis, followed by myeloablative conditioning, which carry their own risks. During the clinical studies, the safety profiles of these interventions were consistent with their known safety and tolerability.

For more information about Libmeldy, please see the Summary of Product Characteristics (SmPC) available on the European Medicines Agency (EMA) website.

Libmeldy is not approved outside of the European Union, UK, Iceland, Liechtenstein, and Norway. OTL-200 is an investigational therapy in the U.S.

Libmeldy was developed in partnership with the San Raffaele-Telethon Institute for Gene Therapy (SR-Tiget) 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, interim data on clinical outcomes for OTL-203 in MPS-I, encouraging preliminary biomarker data for OTL-201 in MPS-IIIA and natural history data in MLD supporting patient identification and market access, 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 September 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**
Christine Harrison
Vice President, Corporate Affairs
+1 202-415-0137
media@orchard-tx.com