Orchard Therapeutics Announces Promising Early Neurocognitive Outcomes from Ongoing Proof-of-concept Study of OTL-201 in MPS-IIIA

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All patients achieved sustained engraftment and supraphysiological SGSH enzyme levels with median 1.5 years follow-up

Four out of five patients demonstrated gain of cognitive skills in line with development in healthy children with one patient showing a marked improvement compared to disease natural history

Treatment with OTL-201 was generally well-tolerated

Company to host conference call and webcast at 5:00 p.m. EST

BOSTON and LONDON, Dec. 12, 2022 (GLOBE NEWSWIRE) -- Orchard Therapeutics (Nasdaq: ORTX), a global gene therapy leader, today announced early clinical findings, including the first neurocognitive results, from its ongoing proof-of-concept (PoC) study of OTL-201, an investigational hematopoietic stem cell (HSC) gene therapy being developed for the treatment of mucopolysaccharidosis type IIIA (MPS-IIIA), also known as Sanfilippo syndrome type A. The data are being featured as part of an oral presentation at the ongoing 64th American Society of Hematology (ASH) Annual Meeting & Exposition in New Orleans.

“These are encouraging results for children living with MPS-IIIA and their families, who currently have no effective treatment options,” said Professor Robert Wynn, chief investigator at The Royal Manchester Children’s Hospital, part of Manchester University NHS Foundation Trust (MFT). “In addition to sustained engraftment of gene-corrected cells and supraphysiological SGSH enzyme levels in the periphery, the early neurocognitive findings show most patients are gaining skills in line with the development of healthy children. In one patient, we also have seen a marked improvement from disease natural history, and we hope to see similar results in the other patients with longer follow-up.”

The oral presentation at ASH 2022 will showcase the first neurocognitive data for all five patients enrolled in the trial and extend upon previously presented biochemical results. Trial patients were 6 to 24 months of age at the time of administration of OTL-201, and the preliminary results are based on a median follow-up of 1.5 years (range: 9-24 months).

Specifically, the biochemical results show the following in all patients:

- Engraftment is sustained to date, with supraphysiological levels of N-sulphoglucosamine sulphohydrolase (SGSH) enzyme measurable in leukocytes 38- to 91-fold above median normal range at one-month post-treatment.
- Supraphysiological SGSH levels were also rapidly detected in $CD15^+$ cells, $CD3^+$ cells, and plasma and have been maintained through the last follow-up visit for each patient. SGSH levels in cerebrospinal fluid (CSF) were within or above normal range by 6-months post-treatment and at the most recent follow-up.
- Abnormal heparan sulfate levels at baseline were rapidly reduced post-treatment in urine (>90 percent), plasma (>82 percent), as well as CSF, and has continued to be maintained at these levels in all evaluated patients.

Early neurocognitive outcomes also indicate that:

- Since receiving the investigational gene therapy, four out of five patients showed gain of cognitive skills in line with development in healthy children compared to natural history of MPS-IIIA.[i]
    - A marked improvement compared with natural history of the disease was observed in one patient at 18 months of follow up.
    - Three additional patients are currently within the normal development quotient (DQ) range at 9 to 18 months post-treatment but require longer follow-up to assess outcomes.
    - Gain of cognitive skills is assessed in this study through evidence of speech acquisition, continence and complex play requiring concentration.

Treatment with OTL-201 was generally well-tolerated in the initial study population. Of the six serious adverse events (SAEs) reported to date, four were thought to be due to conditioning or leukapheresis and one was related to background disease. One patient had delayed platelet engraftment until day 52 post-treatment likely due to Cytomegalovirus infection around the time of infusion. The lentiviral vector integration profile was consistent

with other lentiviral-based HSC gene therapy studies and there has been no indication of insertional oncogenesis and no evidence of clonal dominance due to integration into oncogenes in samples analyzed to date.

“These promising findings continue to demonstrate the ability of our HSC gene therapy platform to enable the migration of gene-corrected cells into the central nervous system and the localized delivery of therapeutic enzymes and proteins to the brain to potentially correct neurodegeneration in multiple severe conditions, building on our programs in metachromatic leukodystrophy and MPS-IH,” said Leslie Meltzer, Ph.D., chief medical officer of Orchard Therapeutics. “While these early results are encouraging, longer follow up is needed as the majority of the patients in this trial have not reached the age where the most severe stages of disease progression typically manifest. We are working with our collaborators at The University of Manchester and Royal Manchester Children’s Hospital to continue following patients in this ongoing study and more fully characterize the clinical profile of OTL-201.”

Five patients aged 6 to 24 months, with a rapidly progressive MPS-IIIA phenotype confirmed by an independent metabolic disease expert, were administered investigational OTL-201 as part of this ongoing PoC trial, sponsored by The University of Manchester (UoM), conducted at Royal Manchester Children’s Hospital, and funded by Orchard Therapeutics. Primary study objectives include safety, tolerability and peripheral expression of SGSH in total leukocytes at 12 months. Secondary study objectives include overall survival and neurocognition as measured by the Bayley Scales of Infant and Toddler Development (BSID-III) or the Kaufman Assessment Battery for Children (KABC-II). The OTL-201 program and this investigator-led clinical trial follow over a decade of development and pre-clinical work by Brian Bigger, Ph.D., professor of cell and gene therapy at UoM.

Patients enrolled in the ongoing PoC trial will be followed for a minimum of three years during which time the study investigators will continue to report additional biochemical and clinical outcomes. The OTL-201 program in MPS-IIIA presents multiple development and commercial synergies with Orchard’s other neurometabolic programs, and the condition represents a significant medical need given there are no approved therapies and treatment with allogeneic HSC transplant has not been shown to be effective for MPS-IIIA patients.

Conference Call and Webcast
A live webcast will be available under "News & Events" in the Investors & Media section of the company's website at www.orchard-tx.com. A replay of the webcast will be archived on the Orchard website following the presentation.

About 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, when healthy, helps the body break down sugar molecules called mucopolysaccharides. The buildup of mucopolysaccharides in the brain and other tissues leads to intellectual disability and loss of motor function. MPS-IIIA occurs in approximately one in every 100,000 live births. Life expectancy of children born with MPS-IIIA is estimated to be between 10-25 years.

About OTL-201
OTL-201 is an investigational hematopoietic stem cell gene therapy being developed for the treatment of MPS-IIIA. It uses a lentiviral vector to insert a functional copy of the human *SGSH* gene into a patient’s hematopoietic stem cells. OTL-201 has received rare pediatric disease designation from the U.S. Food and Drug Administration (FDA) and is currently being evaluated in an ongoing proof-of-concept clinical trial.

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 Twitter and LinkedIn.

About Manchester University NHS Foundation Trust (MFT)
Manchester University NHS Foundation Trust (MFT) is the largest NHS trust in England and a leading provider of specialist healthcare services. Its 10 hospitals are home to hundreds of world class clinicians and academic staff, committed to finding patients the best care and treatments. Its hospitals are Manchester Royal Infirmary, Saint Mary's Hospital, Royal Manchester Children's Hospital, Manchester Royal Eye Hospital, North Manchester General Hospital, University Dental Hospital of Manchester, Trafford General Hospital, Altrincham Hospital, Wythenshawe Hospital and Withington Hospital. More information is available at: www.mft.nhs.uk.

About The University of Manchester
The University of Manchester is a member of the prestigious Russell Group and one of the UK’s largest single-site universities. We have over 40,000 students, 12,000 staff and, with almost 480,000 former students from more than 190 countries, are home to the largest alumni community of any campus-based university in the UK. We are ranked in the top ten of the Times Higher Education (THE) Impact Rankings globally; are the top UK University for graduate employability according to The Graduate Market in 2022 and no fewer than 25 Nobel laureates have either worked or studied here. Visit www.manchester.ac.uk for further information or https://www.manchester.ac.uk/discover/vision/ for our latest strategic vision.

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 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, Orchard's business and product development strategy and goals, including the therapeutic potential of OTL-201, Orchard's expectations with respect to regulatory submissions for its product candidates, including OTL-201, and Orchard's expectations regarding its ongoing preclinical and clinical trials, including the timing of enrollment for clinical trials and release of additional preclinical and clinical data, and the likelihood that data from clinical trials will be positive and support further clinical development and regulatory approval of Orchard's 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 prior results, such as signals of safety, activity or durability of effect, observed from clinical trials of OTL-201 will not continue or be repeated in Orchard's ongoing or planned clinical trials of OTL-201, will be insufficient to support regulatory submissions or support or maintain marketing approval in the US or European Union, or that long-term adverse safety findings may be discovered; and the risk that any one or more of Orchard's product candidates, including the OTL-201, will not be approved, successfully developed or commercialized. 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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[i] *Cognitive function measured via standard scores, age-equivalent scores, development quotient (DQ) and gross scale equivalent [BSID-III] or [KABC-II]*

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