Orchard Therapeutics Presents Data from Research Programs at ASGCT Demonstrating the Ability of HSC Gene Therapy to Address Larger Indications

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Preclinical proof-of-concept data show the therapeutic potential of OTL-104 for NOD2 Crohn's disease, a severe and treatment-refractory form of the disease

In vivo data demonstrate the development of CAR-Treg cells from genetically engineered HSCs as a potential one-time treatment for autoimmune disorders

Company to host conference call and webcast Tuesday, May 23 at 8:00 a.m. EDT

BOSTON and LONDON, May 18, 2023 (GLOBE NEWSWIRE) -- Orchard Therapeutics (Nasdaq: ORTX), a global gene therapy leader, today presented new data from the company's hematopoietic stem cell (HSC) gene therapy research pipeline targeting larger indications at the ongoing 26th Annual Meeting of the American Society of Gene and Cell Therapy (ASGCT) in Los Angeles. Presentations include preclinical proof-of-concept data from OTL-104, the company's investigational HSC gene therapy for the treatment of nucleotide-binding oligomerization domain containing protein 2 (NOD2) Crohn's disease, as well as *in vivo* preclinical data demonstrating the development of functional CAR-Treg cells from genetically engineered HSCs. Both programs were designed and developed in Orchard's own research laboratories utilizing the company's proprietary HSC gene therapy platform.

"These data continue to demonstrate the power of our HSC gene therapy platform and its applicability beyond our rare neurometabolic franchise into diseases with larger patient populations," said Fulvio Mavilio, Ph.D., chief scientific officer of Orchard Therapeutics. "Due to their unique ability to self-renew and differentiate into multiple cell types that migrate to tissues and organs often inaccessible to other therapeutic modalities, HSC-based gene therapies have immense therapeutic and collaborative potential. We look forward to advancing IND-enabling activities for our research program in NOD2 Crohn's disease and further developing the HSC-derived CAR-Treg cell technology."

OTL-104 (NOD2 Crohn's Disease) Preclinical Data Summary

Using established *in vitro* and *in vivo* models of NOD2 deficiency, including NOD2 knockout mice and HSC-derived macrophages from Crohn's patients with biallelic NOD2 mutations, Orchard researchers evaluated the safety and efficacy of HSC gene therapy in restoring NOD2-dependent immune responses. The chimeric promoter used in OTL-104 was originally developed and clinically tested in patients with X-linked chronic granulomatous disease (X-CGD), where enhanced expression of gp91-Phox in myeloid and monocyte lineages was demonstrated.

In a poster session tomorrow, the first preclinical proof-of-concept data will highlight the therapeutic potential of this approach, including:

- OTL-104, a lentiviral vector expressing NOD2 under the control of a myeloid-directed chimeric promoter, fully restores NOD2-dependent immune responses in macrophages derived from HSCs obtained from Crohn's patients carrying biallelic NOD2 mutations to within the range of healthy donor cells.
- Transplantation of OTL-104 in NOD2 knockout mice reconstitutes NOD2 expression in intestinal tissue resident cells and broadly restores NOD2-dependent innate immune cell functions.

Taken together, these results confirm the negative impact of NOD2 deficiency in primary immune activation and support the therapeutic potential of HSC gene therapy to provide long-term correction of NOD2 Crohn's disease. Work to evaluate OTL-104's ability to correct an induced NOD2 knockout mouse model of ileitis is currently ongoing. The company expects to commence IND- and CTA-enabling studies in the second half of 2023, with a potential filing now anticipated in the first half of 2025.

HSC CAR-Treg cell Technology Preclinical Data Summary

Yesterday's poster session demonstrates the feasibility of utilizing HSC gene therapy to provide stable and targeted immunotherapy, through the ability of HSCs to differentiate into T regulatory (Treg) cells engineered to express chimeric antigen-specific receptors (CAR). This approach combines the proven durability of HSC gene therapy with the specific suppressive activity of CAR-Treg cells, providing an alternative to current treatments which fail to effectively control chronic autoimmune diseases, such as multiple sclerosis, rheumatoid arthritis and Type 1 diabetes.

Data from transplanted mice show that the preferential expression of CAR in HSC-derived regulatory T cells *in vivo* does not significantly alter the development, phenotype or function of these suppressive immune cells. Also, the functionality of the CAR receptor is demonstrated when HSC-derived CAR-Tregs can be activated *ex vivo* by exposure to a CAR-specific ligand, producing the immunosuppressive cytokine IL-10.

The company will continue to advance its preclinical research activities aimed at further demonstrating the feasibility and applicability of its HSC CAR-Treg cell technology.

Conference Call and Webcast
A live webcast to recap the data will be available under "News & Events" in the Investors & Media section of the company's website at www.orchard-tx.com on Tuesday May 23, 2023, at 8:00 a.m. EDT. A replay of the webcast will be archived on the Orchard website following the presentation.

About OTL-104 and NOD2 Crohn's Disease
Crohn's disease is a form of Inflammatory Bowel Disease (IBD), a condition affecting the gastrointestinal tract. Mutations in a number of genes are known to confer susceptibility to the risk of Crohn's, and among these the nucleotide-binding oligomerization domain-containing protein 2 (NOD2) gene is the most common genetic factor. NOD2 deficiency results in an impaired detection and clearance of bacteria penetrating the gut during gastrointestinal infection. This leads to a form of Crohn's disease more severe and refractory to existing therapies, with manifestations including chronic abdominal pain, diarrhea, weight loss, fatigue, malnutrition and for some patients, more severe intestinal damage requiring surgical resection. Epidemiological studies suggest NOD2 genetic variants causing functional defects are associated with 7 to 10% of all cases of Crohn's, with up to 200,000 patients in the U.S. and Europe with two NOD2 mutated alleles.

There is currently no cure for Crohn's disease, and long-term, effective treatment options are limited. Current clinical management for Crohn's disease includes use of immune-suppressive medications, biological agents such as anti-TNF, steroids and surgical resection.

OTL-104 is an investigational HSC gene therapy in development for the potential treatment of patients with NOD2 Crohn's disease. As the pathogenesis of NOD2 Crohn's disease is associated with the function of cells of the hematopoietic system, OTL-104 may therefore be used to restore NOD2 function to immune cells such as tissue resident macrophages within the gastrointestinal tract. OTL-104 is designed to introduce the NOD2 gene into cells of the hematopoietic system by lentiviral transduction of a patient's own HSCs, and the gene-modified cells can then be infused back into the patient.

About Orchard's Proprietary HSC T-reg Cell Technology
HSC gene therapy is well-suited to address severe autoimmune disorders due to the ability of HSCs to differentiate into regulatory T-cells (Tregs) which are a specialized subset of T-cells that can suppress inflammation and be harnessed as a cell therapy with an approach similar to that used to create chimeric antigen receptor T-cells (CAR-Ts). Orchard's approach aims to combine the demonstrated durability of HSC gene therapy in genetic diseases with the specific suppressive potential of Tregs. Orchard has established a proprietary position covering the concept, therapeutic application and specifics of HSC-antigen-specific Treg therapy.

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 preclinical, 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 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 the programs mentioned in this press release, Orchard's expectations with respect to regulatory submissions for its product candidates, 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 will not continue or be repeated in Orchard's ongoing or planned clinical trials, 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 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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