



## **Orchard Therapeutics Outlines Differentiated Profile of Its HSC Gene Therapy Approach and Discusses Potential Future Applications at Virtual R&D Investor Event**

September 14, 2021

*Novel Discovery Research in HSC-generated Antigen-specific Regulatory T Cells Disclosed*

*HSC Gene Therapy Also Provides Advantages for Delivery of Monoclonal Antibodies*

*New Applications Present Opportunities for Future Partnerships*

BOSTON and LONDON, Sept. 14, 2021 (GLOBE NEWSWIRE) -- Orchard Therapeutics (Nasdaq: ORTX), a global gene therapy leader, today will present on the company's discovery and research efforts in hematopoietic stem cell (HSC) gene therapy, including an update on the OTL-104 program in development for NOD2 Crohn's disease (NOD2-CD), together with overviews of potential new applications in the areas of HSC-generated antigen-specific regulatory T cells (Tregs) and HSC-vectorization of monoclonal antibodies (mAbs). A live webcast of the presentation will be available in the Investors & Media section of the company's website at [www.orchard-tx.com](http://www.orchard-tx.com) today at 7:00 a.m. ET.

"Today, we present the next chapter in Orchard's journey as a leader in HSC gene therapy, including our work in larger indications such as Crohn's disease and enabling technologies," said Bobby Gaspar, M.D., Ph.D., chief executive officer, Orchard Therapeutics. "These new initiatives build on the strategy we laid out 18 months ago to leverage the power of our HSC gene therapy platform approach beyond ultra-rare diseases. Our discovery work is based on the same scientific approach supported by clinical data in more than 160 patients treated across multiple genetic diseases in our current and former programs and an EMA approval for Libmeldy™. We believe that Orchard's HSC gene therapy is truly differentiated in terms of efficacy and safety, and we are excited about the possibilities with its expanded application into larger indications."

### **Differentiated Profile of Orchard's HSC Gene Therapy Approach**

The company is progressing an advanced portfolio that has achieved approval from the European Commission for Libmeldy™ (OTL-200) for eligible MLD patients and demonstrated proof-of-concept in five other indications. In pre-clinical and clinical studies to date, Orchard's HSC gene therapy approach has exhibited a differentiated profile consisting of favorable safety, long-term durability and broad treatment applicability. Specifically:

- Orchard's lentiviral vector-based HSC gene therapy programs have shown no indication of oncogenesis and no evidence of clonal dominance due to integration into oncogenes. Importantly, the promoters and regulatory elements of Orchard vectors are derived from human (not viral) sequences and are specifically designed to have limited enhancer activity on neighboring genes thereby mitigating the potential for safety concerns.
- More than 160 patients have been treated in Orchard's current and former lentiviral vector-based HSC gene therapy programs, with duration of treatment effect of over 10 years in the earliest treated patients and more than 750 combined years of patient experience.
- Because of the fundamental biological differences between the HSC and adeno-associated virus (AAV) gene therapy approaches, Orchard's programs have not, to date, seen the safety concerns experienced by the AAV gene therapy field. Due to the autologous nature of Orchard's HSC gene therapy and the lack of direct patient exposure to the viral vector, no patients are automatically excluded from receiving treatment due to potential immune reactions to the drug product.

### **Updates from OTL-104 Program in NOD2-CD**

Orchard is continuing its work to exploit the curative potential of HSC gene therapy by applying its approach to more prevalent conditions where there is a compelling scientific rationale. One area of focus is in a subset of Crohn's disease patients who have mutations in both copies of the NOD2 gene and typically present with a more severe and untreatable form of the disease. OTL-104 pre-clinical work completed to date demonstrates that:

- Restoration of NOD2 protein expression in murine and human stem cells can rescue a defective myeloid immune response to microbial peptides.
- NOD2 defective inflammatory functions in primary human cells can be restored by both lentiviral and gene editing approaches.
- NOD2-LV gene modification of human CD34+ stem cells does not affect HSC engraftment or immune subset development and differentiation.
- HSC transplantation demonstrates that gene-modified cells can efficiently migrate and engraft into the intestinal tissue.

Development of an experimental colitis induction model is now in progress for OTL-104 pre-clinical proof-of-concept studies. The promising data highlighted above supports the continued advancement of OTL-104 toward IND-enabling toxicology and biodistribution studies.

### **New Technology Applications: HSC-generated Antigen-specific Tregs and HSC-vectorization of mAbs**

HSC gene therapy is well-suited to expand into severe autoimmune disorders due to the ability of HSCs to differentiate into Tregs, which are a

specialized subset of T cells that can suppress inflammation and be harnessed as a cell therapy (similar to 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. In addition, Orchard is pursuing the application of HSC vectorization of mAbs, which has potential advantages over standard administration in terms of efficacy and improved targeting within tissues due to the migration of gene modified HSCs. These new areas of research could represent significant commercial opportunities in large indications for Orchard alone or with potential partners interested in utilizing the HSC gene therapy approach.

### **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 has a deep 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](http://www.orchard-tx.com), and follow us on [Twitter](#) and [LinkedIn](#).

### **About Libmeldy / OTL-200**

Libmeldy (atidarsagene autotemcel), 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 EMA website.

Libmeldy is approved in the European Union, UK, Iceland, Liechtenstein and Norway. OTL-200 is an investigational therapy in the US.

Libmeldy was developed in partnership with the San Raffaele-Telethon Institute for Gene Therapy (SR-Tiget) in Milan, Italy.

### **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](http://www.orchard-tx.com)), the investor relations website ([ir.orchard-tx.com](http://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, including with respect to its expected future milestones, and its plans and expectations for the development of its product candidates, including the product candidates referred to in this release, and the therapeutic and commercial potential of 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 risk that any one or more of Orchard's product candidates, including the product candidates referred to in this release, will not be approved, successfully developed or commercialized; the risk that prior results, such as signals of safety, activity or durability of effect, observed from preclinical studies or clinical trials of Orchard's product candidates will not be repeated or continue in ongoing or future studies or trials involving its product candidates; the risk that the market opportunity for its product candidates may be lower than estimated; and the severity of the impact of the COVID-19 pandemic on Orchard's business, including on preclinical and clinical development, its supply chain and commercial programs. 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, 2021, 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](mailto:Renee.Leck@orchard-tx.com)

**Media**

Benjamin Navon

Director, Corporate Communications

+1 857-248-9454

[Benjamin.Navon@orchard-tx.com](mailto:Benjamin.Navon@orchard-tx.com)