Orchard Therapeutics Unveils Details on New HSC Gene Therapy Research Programs as Part of R&D Investor Event Tomorrow at 9:00 a.m. ET

November 12, 2020

First look at preclinical data in frontotemporal dementia with progranulin mutations (GRN-FTD) and new amyotrophic lateral sclerosis (ALS) program

NOD2 mutation revealed as Crohn's disease (CD) genetic target, associated with 7-10% of all CD cases in the U.S. and Europe

Deep dive on transduction enhancers and stable cell line technology innovations that support manufacturing for larger indications

BOSTON and LONDON, Nov. 12, 2020 (GLOBE NEWSWIRE) -- Orchard Therapeutics (Nasdaq: ORTX), a global gene therapy leader, today previewed details on its investigational hematopoietic stem cell (HSC) gene therapy research programs in GRN-FTD and NOD2-CD in advance of an upcoming virtual R&D investor event. The company also disclosed a new research program in ALS. A live webcast of the presentation will be available in the Investors & Media section of the company's website at www.orchard-tx.com starting Friday, November 13, 2020 at 9:00 a.m. ET.

"We are excited to draw back the curtain at tomorrow's event on our work in larger indications that form an important part of Orchard's evolution as a company, including a new program in ALS, in addition to our work in genetic subsets of FTD and Crohn's disease," said Bobby Gaspar, M.D., Ph.D., chief executive officer, Orchard Therapeutics. "These research programs have been established using a scientific approach that has resulted in more than 160 patients being treated across multiple rare diseases and a recent positive CHMP opinion in the EU for Libmeldy™. We believe that HSC gene therapy has the power to transform lives, and we are excited about the possibilities for Orchard and patients with its expanded application."

OTL-204 for GRN-FTD and new ALS research program

The GRN-FTD and ALS programs are based on the same HSC gene therapy approach that has been clinically validated with Libmeldy (OTL-200), Orchard's program for metachromatic leukodystrophy, and is under clinical evaluation in the OTL-203 and OTL-201 programs for mucopolysaccharidosis type I and mucopolysaccharidosis type IIIA, respectively. Development work in GRN-FTD and ALS will be undertaken as part of a collaboration with Boston Children's Hospital (BCH), the University of Padua (UNIPD) and Prof. Alessandra Biffi, chair of the Pediatric Hematology, Oncology and Stem Cell Transplant Division at UNIPD and co-director of the Gene Therapy Program at BCH.

- OTL-204 for GRN-FTD: Orchard's preclinical program in GRN-FTD seeks to introduce a working copy of the *GRN* gene into HSCs, which can differentiate into microglia and secrete progranulin in the central nervous system, potentially correcting the underlying cause of the disease.
    - Preclinical work completed to date demonstrates that gene-modified HSCs can lead to GRN expression and secretion in the culture medium and uptake by GRN-negative cells.
    - Epidemiological studies suggest the FTD prevalent population in the U.S. and Europe is more than 50,000 patients with approximately 5% caused by mutations in the *GRN* gene, resulting in up to 2,500 GRN-FTD prevalent patients in the U.S. and Europe, with approximately 800 new patients diagnosed each year.[1]
- ALS research program: Orchard's new gene therapy research program in ALS will aim to restore healthy, non-activated microglia with genetically modified HSCs to favorably modulate neuroinflammation, improve symptoms and prolong survival.
    - Preclinical work previously undertaken by Prof. Biffi at BCH is based on exploiting shRNA mediated suppression of NADPH oxidase 2 (NOX2) activity to modulate neuroinflammation and neurodegeneration.
    - Rather than focusing on restoring gene function in patients with specific genetic susceptibility, this approach targets neuroinflammatory responses to support neuronal survival and could be applicable to a broader population of ALS patients.

Prof. Biffi commented, "The ability of HSC gene therapy to restore healthy microglia function supports the use of this technology for the development of treatments for a variety of diseases with central nervous system involvement. In GRN-FTD, initial *in vitro* data shows progranulin expression and secretion in culture and uptake indicative of cross-correction. My previous work at BCH researching ALS supports the novel approach of treating this severe neurodegenerative condition by targeting the NOX2 pathway."

OTL-104 for NOD2-CD

Orchard's preclinical program in CD targets mutations in the nucleotide-binding oligomerization domain-containing protein 2 (*NOD2*) gene, which plays a role in immune cell response to bacterial peptides in the gastrointestinal (GI) tract. The company's proposed approach leverages this link, using gene modified HSC-derived cells (monocytes) to replace GI resident macrophages, thus potentially correcting the inflammation and colitis associated with NOD2-CD.

- OTL-104 preclinical work completed to date demonstrates successful restoration of NOD2 expression and functional correction in response to bacterial peptide stimulation, in NOD2 defective murine and human cells.

- Epidemiological studies suggest the NOD2 genetic subset is associated with 7-10% of all cases of CD, with up to 200,000 patients in the U.S. and Europe with two NOD2 mutated alleles.[2]

Manufacturing Innovations to Support Work in Larger Indications
Transduction enhancers (TEs) and stable cell line technology (SCLT)

Orchard has completed a thorough TE screening process and identified and validated several novel TE compounds, which in combination, facilitate lentiviral vector entry into HSCs and have shown a greater than 50% reduction in vector requirements. The enhancers' mode of action is expected to be effective in each of Orchard's HSC gene therapy programs. An evaluation of enhancer-treated HSC engraftment potential in mice is currently underway.

The company has worked extensively with SCLT, including the technology licensed from GSK for certain programs, to both develop processes to efficiently create SCLs for new vectors and scale up the production of SCLs to clinical grade. Results have delivered consistent levels of high-titer lentiviral production comparable to those seen using conventional methods. Selection of single high-titer clones for new vectors using this method has been achieved within three months. Work at Orchard is ongoing to develop upstream and downstream processes to further improve productivity and scalability.

"We have a clear roadmap for Orchard's future that prioritizes strategic growth and draws on the many synergies across our scientific, manufacturing and emerging commercial platforms," said Frank Thomas, president and chief operating officer. "Over the next 12 months we have an array of exciting commercial, regulatory and clinical milestones that will continue to showcase the breadth and depth of our advanced HSC gene therapy portfolio."

Webcast Information

A live webcast of the presentation "New Horizons in Gene Therapy" will be 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 on the Orchard website following the presentation.

About Orchard's Research Collaborations

In connection with its previously disclosed collaboration with Prof. Alessandra Biffi, Orchard has signed agreements with Boston Children's Hospital and the University of Padua to develop and exclusively license new *ex vivo* HSC gene therapy programs, patents and technologies for the treatment of neurodegenerative disorders. As part of the collaboration, Orchard has initiated sponsored research agreements and obtained exclusive options to license multiple new preclinical programs, including frontotemporal dementia with progranulin mutations (GRN-FTD), amyotrophic lateral sclerosis (ALS) and other rare and less rare indications. Orchard continues to support Professor Biffi's labs in the development of new proprietary technology focused on enhancing the application of gene-modified HSC therapy for CNS disorders.

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, including with respect to its manufacturing strategy, 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 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

[1] Knopman DS, Roberts RO. J Mol Neurosci. 2011, Onyike CU, Diehl-Schmid J. Int Rev Psychiatry. 2013 and Riedl L, et al Neuropsychiatr Dis Treat. 2014

[2] Centers for Disease Control and Prevention; European Crohn’s and Colitis Organisation (ECCO); Ashton, James J et al.Clin Transl Gastroenterol. 2020 Feb

Source: Orchard Therapeutics (Europe) Limited