Orchard Therapeutics to Present New Registrational Data of Investigational Gene Therapies at the 61st American Society of Hematology Annual Meeting

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Registrational Trial for Wiskott-Aldrich Syndrome Met Key Primary and Secondary Endpoints at Three Years; Data from Integrated Analysis Reinforce Treatment Benefits of Gene Therapy and Durability of Effect in Additional Patients

Similar Profiles Reported Between Cryopreserved and Fresh Formulations of OTL-101, Further Supporting Upcoming Regulatory Filing and Broad Patient Availability

BOSTON and LONDON, Nov. 06, 2019 (GLOBE NEWSWIRE) -- Orchard Therapeutics (Nasdaq: ORTX), a leading commercial-stage biopharmaceutical company dedicated to transforming the lives of patients with serious and life-threatening rare diseases through innovative gene therapies, today announced the upcoming presentation of registrational data from multiple programs at the 61st American Society of Hematology (ASH) Annual Meeting in Orlando, FL.

Investigators will describe ongoing clinical progress for two lead development programs in the company's primary immune deficiencies portfolio: OTL-103, an investigational gene therapy in development for the treatment of Wiskott-Aldrich syndrome (WAS) at the San Raffaele-Telethon Institute for Gene Therapy (SR-Tiget) in Milan, Italy; and OTL-101, an investigational gene therapy in development for the treatment of adenosine deaminase severe combined immunodeficiency (ADA-SCID).

In addition, investigators will deliver an oral presentation featuring updated data from the ongoing proof-of-concept study of OTL-203, an investigational gene therapy in development for the treatment of mucopolysaccharidosis type I (MPS-I) at SR-Tiget.

"This growing body of positive data, from dozens of patients across multiple diseases, provides a solid foundation as we advance each program toward its next phase of development, including upcoming regulatory submissions for ADA-SCID and WAS," said Mark Rothera, president and chief executive officer of Orchard Therapeutics. "We now have two supportive data sets — one from our OTL-101 program in ADA-SCID and one from our OTL-200 program in metachromatic leukodystrophy — that demonstrate cryopreserved formulations are engrafting as expected, similar to the fresh formulation. This supports our strategy for making these therapies, if approved, broadly available to patients in need throughout the world."

"We are extremely pleased with our continued clinical progress, including the duration of benefits seen in our WAS trial, which is the longest published follow-up of hematopoietic stem cell gene therapy durability to date using lentiviral vector transduction," said Bobby Gaspar, M.D., Ph.D., chief scientific officer of Orchard Therapeutics. "The totality of these data underscores the broad applicability of our gene therapy platform approach and the opportunity we have to deliver potentially curative treatments for a variety of devastating and rare genetic disorders."

Full presentation details are below:

Poster Presentation Details

Lentiviral Hematopoietic Stem and Progenitor Cell Gene Therapy for Wiskott-Aldrich Syndrome (WAS): Up to 8 Years of Follow up in 17 Subjects Treated Since 2010
Publication Number: 3346
Session: 801. Gene Therapy and Transfer: Poster II
Date and time: Sunday, December 8, 6:00-8:00pm ET

This presentation includes results from an integrated analysis of 17 patients treated with OTL-103 for the treatment of WAS, including the complete data set for the eight patients from the registrational study and nine who received OTL-103 as part of an expanded access program (EAP). Participants have been followed for a median of three years.

In the eight-patient registrational trial, investigators reported that the study achieved its key primary and secondary endpoints at three years, including the elimination of severe bleeding episodes and a significant reduction in the frequency of moderate bleeding episodes. Successful engraftment was observed within three months, leading to an increase in WAS protein expression and a vector copy number that has been maintained for up to eight years. Nine months post-administration, all patients stopped receiving platelet transfusions, and no severe bleeding events were reported. A significant reduction in the rate of severe infections was also observed and all patients were able to stop immunoglobin replacement therapy (IgRT), suggesting a complete reconstitution of immune function with durability of effect of up to eight years of follow-up post-gene therapy.

Similar clinical results were seen in the integrated analysis of 17 patients and overall survival was 94% (16/17). One death occurred among the EAP cohort that was considered by the investigator to be unrelated to OTL-103.

Across the original and integrated data sets, there were no adverse events considered to be related to OTL-103, including no evidence of oncogenesis, replication competent lentivirus or abnormal clonal proliferation. Clinical benefit was also attained in patients older than five years of age, a group considered at higher risk when treated with allogeneic hematopoietic stem cell transplantation (HSCT).

Lentiviral Gene Therapy with Autologous Hematopoietic Stem and Progenitor Cells (HSPCs) for the Treatment of Severe Combined Immune Deficiency Due to Adenosine Deaminase Deficiency (ADA-SCID): Results in an Expanded Cohort
Publication Number: 3345
Session: 801. Gene Therapy and Transfer: Poster II

Date and time: Sunday, December 8, 6:00-8:00pm ET

This presentation details the safety and efficacy of OTL-101 in 30 individuals with ADA-SCID, treated with either fresh (n=20) or cryopreserved (n=10) formulations. Patients were followed for a median of 24 months (range 12-24 months overall and 12-18 months for patients treated with the cryopreserved formulation), and results were compared with a historical cohort of 26 ADA-SCID patients treated with allogeneic hematopoietic stem cell transplantation (HSCT), including HSCT both with, and without, a matched related donor.

Results showed engraftment of genetically modified hematopoietic stem cells in 29 of 30 OTL-101 patients by six to eight months, which persisted through follow-up in both studies. Analysis of both the vector copy number in granulocytes (a measure of engraftment) and T-cell reconstitution (a relevant measure of immune recovery) showed consistent performance across the fresh and cryopreserved-treated patients.

In the OTL-101 treated patients, overall survival was 30/30 (100%) and event-free survival was 29/30 (97%). One of the 30 patients restarted treatment with enzyme replacement therapy (ERT) and subsequently withdrew from the study and received a rescue HSCT. In the historical control population, 42% of HSCT patients required re-initiation of ERT, rescue HSCT or other intervention, or died. As expected, there was no incidence of graft versus host disease in the OTL-101 group, compared with eight patients who received HSCT.

Eighteen of 20 patients (90%) in the fresh formulation study stopped immunoglobin replacement therapy (IgRT) after two years, compared to 52% of HSCT patients. Of the seven patients treated with the cryopreserved formulation with 18 months of follow-up, five had discontinued IgRT (71%), which is comparable to the 18-month data for patients treated with the fresh formulation.

Oral Presentation Details

Extensive Metabolic Correction of Hurler Disease by Hematopoietic Stem Cell-Based Gene Therapy: Preliminary Results from a Phase I/II Trial
Publication Number: 607
Session: 801. Gene Therapy and Transfer: Gene Therapies for Non-Malignant Disorders
Date and time: Monday, December 9, 7:00am ET

Investigators will present updated analyses from the ongoing proof-of-concept trial of OTL-203 for mucopolysaccharidosis type I (MPS-I).

About ADA-SCID and OTL-101
Severe combined immune deficiency due to adenosine deaminase deficiency (ADA-SCID) is a rare, life-threatening, inherited disease of the immune system caused by mutations in the ADA gene resulting in a lack of, or minimal, immune system development.[1-4] The first symptoms of ADA-SCID typically manifest during infancy with recurrent severe bacterial, viral and fungal infections and overall failure to thrive, and without treatment the condition can be fatal within the first two years of life. The incidence of ADA-SCID is currently estimated to be one in 500,000 live births in the United States and between one in 200,000 and one in 1 million in Europe.[3] OTL-101 is an autologous, *ex vivo,* hematopoietic stem cell-based gene therapy for the treatment of patients diagnosed with ADA-SCID being investigated in multiple clinical trials in the United States and Europe, including a registrational trial at the University of California, Los Angeles (UCLA). OTL-101 has received orphan drug designation from the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for the treatment of ADA-SCID, and Breakthrough Therapy Designation from the FDA.

About WAS and OTL-103
Wiskott-Aldrich Syndrome (WAS) is a life-threatening inherited immune disorder characterized by autoimmunity and abnormal platelet function and manifests with recurrent, severe infections and severe bleeding episodes, which are the leading causes of death in this disease. Without treatment, the median survival for WAS patients is 14 years of age. Treatment with stem cell transplant carries significant risk of mortality and morbidities. OTL-103 is an *ex vivo,* autologous, hematopoietic stem cell-based gene therapy developed for the treatment of WAS that Orchard acquired from GSK in April 2018 and has been developed at the San Raffaele-Telethon Institute for Gene Therapy (SR-Tiget) in Milan, Italy. The global incidence of WAS is estimated to be about 100-260 births per year, with a global prevalence of 2,900-4,700 patients.

About MPS-I and OTL-203
Mucopolysaccharidosis type I (MPS-I) is a rare inherited neurometabolic disease caused by a deficiency of the IDUA (alpha-L-iduronidase) lysosomal enzyme required to break down glycosaminoglycans (also known as GAGs or mucopolysaccharides). The accumulation of GAGs across multiple organ systems results in the symptoms of MPS-I including neurocognitive impairment, skeletal deformity, loss of vision and hearing, hydrocephalus, and cardiovascular and pulmonary complications. MPS-I occurs at an overall estimated frequency of one in every 100,000 live births.[5] There are three subtypes of MPS-I; approximately 60 percent of MPS-I patients have the severe Hurler subtype and, when untreated, these patients rarely live past the age of 10.[Id] 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 *ex vivo*, autologous, hematopoietic stem cell-based 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 Orchard
Orchard Therapeutics is a fully integrated commercial-stage biopharmaceutical company dedicated to transforming the lives of patients with serious and life-threatening rare diseases through innovative gene therapies.

Orchard's portfolio of *ex vivo*, autologous, hematopoietic stem cell (HSC) based gene therapies includes Strimvelis®, a gammaretroviral vector-based gene therapy and the first such treatment approved by the European Medicines Agency for severe combined immune deficiency due to adenosine deaminase deficiency (ADA-SCID). Additional programs for neurometabolic disorders, primary immune deficiencies and hemoglobinopathies are all based on lentiviral vector-based gene modification of autologous HSCs and include three advanced registrational studies for metachromatic leukodystrophy (MLD), ADA-SCID and Wiskott-Aldrich syndrome (WAS), clinical programs for X-linked chronic granulomatous disease (X-CGD), transfusion-dependent beta-thalassemia (TDT) and mucopolysaccharidosis type I (MPS-I), as well as an extensive preclinical pipeline. Strimvelis, as well as the programs in MLD, WAS and TDT were acquired by Orchard from GSK in April 2018 and originated from a pioneering collaboration between GSK and the San Raffaele Telethon Institute for Gene Therapy in Milan, Italy initiated in 2010.

Orchard currently has offices in the UK and the U.S., including London, San Francisco and Boston.

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," "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, the therapeutic potential of Orchard's product candidates, including the product candidate or candidates referred to in this release, Orchard's expectations regarding the timing of regulatory submissions for approval of its product candidates, including the product candidate or candidates referred to in this release, 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, including any cryopreserved formulations of such product candidates, and the likelihood of approval of such product candidates by the applicable regulatory authorities. 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, the risks and uncertainties include, without limitation: the risk that any one or more of Orchard's product candidates, including the product candidate or candidates referred to in this release, will not be successfully developed or commercialized, the risk of cessation or delay of any of Orchard's ongoing or planned 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, 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, 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 annual report on Form 20-F for the year ended December 31, 2018 as filed with the U.S. Securities and Exchange Commission (SEC) on March 22, 2019, 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.

[1]Orphanet. SCID due to ADA deficiency. [2]Whitmore KV, Gaspar HB. Front Immunol. 2016;7:314. [3]Kwan A, et al. JAMA. 2014;312:729-738. [4]Sauer AV, et al. Front Immunol. 2012;3:265. [5]Beck et al. The Natural History of MPS I: Global Perspectives from the MPS I Registry. Genetics in Medicine 2014, 16(10), 759.

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