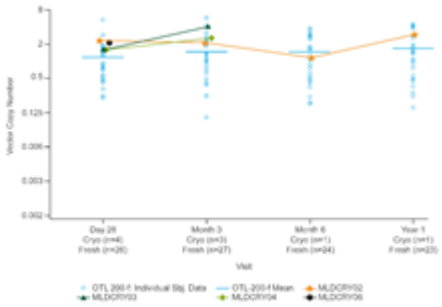
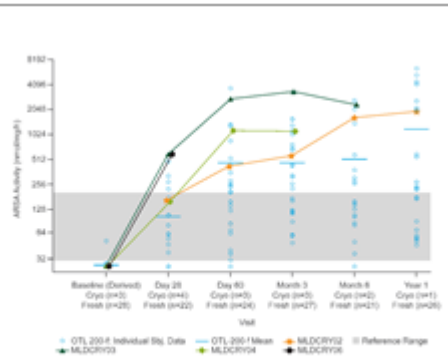
Orchard Therapeutics Presents Data from OTL-200 in Patients with Metachromatic Leukodystrophy Using Cryopreservation

October 22, 2019

Stable Levels of Engraftment and Reconstitution of Enzyme Activity in Patients with Up to 12 Months of Follow-up Indicate Similar Profiles Between Cryopreserved and Fresh Formulations



Profiles of VCN in bone marrow CD34+ cells: OTL-200 cryopreserved vs. OTL-200 fresh



ARSA activity profile in peripheral blood: OTL-200 cryopreserved vs. OTL-200 fresh; c = cryopreserved; f = fresh; Sbj. = subject

Regulatory Submission in Europe Expected in the First Half of 2020 and U.S. Approximately One Year Later

BOSTON and LONDON, Oct. 22, 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 initial results from a clinical trial with a cryopreserved formulation of OTL-200, a gene therapy in development for the treatment of metachromatic leukodystrophy (MLD) at the San Raffaele-Telethon Institute for Gene Therapy (SR-Tiget) in Milan, Italy. The initial data show that cellular engraftment with OTL-200 using a cryopreserved formulation is similar to that observed using a fresh formulation with the longest patient having 12 months of follow-up since treatment. The data are being featured this week in a poster session at the European Society of Gene &

Cell Therapy (ESGCT) Annual Congress in Barcelona, Spain.

MLD is a devastating and rapidly progressing disease with no standard treatment options. In its most severe forms, patients will not survive beyond their first decade of life.

These data compare the initial results of OTL-200 in the first four MLD patients treated using a cryopreserved formulation to a previously presented integrated analysis of 29 patients treated with a fresh formulation that demonstrated meaningful clinical outcomes. Hematopoietic stem cells are collected, purified and transduced in the same way for both formulations. For the cryopreserved formulation, following transduction, the gene-corrected cells are placed in a specific medium that allows them to be stably frozen. After successful testing and release, the cryopreserved cells are shipped to the site of care where they are thawed and administered to patients who have received conditioning.

“Presenting the first supportive data on OTL-200 using a cryopreserved formulation represents a cross-functional effort involving our clinical, CMC and regulatory teams as we prepare for the upcoming European regulatory submission for MLD followed by a BLA in the U.S.,” said Mark Rothera, president and chief executive officer of Orchard. “If approved, a cryopreserved formulation of OTL-200 would more readily facilitate global commercialization and patient access efforts, which are key elements in our mission to deliver potentially curative therapies to patients suffering from often-deadly rare diseases.”

Mr. Rothera continued, “With over 40 patients now treated using a cryopreserved formulation across our pipeline of six clinical-stage programs, we are confident our approach is supported by a robust set of evidence.”

Study Results
At the time of the analysis, four early-onset MLD patients (two late infantile and two early juvenile) have been treated with the cryopreserved formulation of OTL-200. All patients are alive and were followed for a minimum of one month, with the longest follow-up out to 12 months in the first patient treated (median follow-up of 0.38 years). The age at the time of treatment ranged from seven months to 42 months.

The initial results in patients receiving the cryopreserved formulation (n=4) demonstrated the following:

- Stable levels of engraftment of gene-corrected cells, as evidenced by the percent of transduced $CD34^+$ cells in the bone marrow, the vector copy number (VCN) levels in the bone marrow (see Figure 1 below) and the VCN levels in peripheral blood mononuclear cells, were within the range observed in patients treated with the fresh formulation. Engraftment of gene-corrected cells in all patients receiving the cryopreserved formulation was seen one month after treatment and remained stable throughout the length of follow-up for each patient.
- Reconstitution of arylsulfatase-A (ARSA) enzyme activity in the peripheral blood (see Figure 2 below) and cerebrospinal fluid (as a surrogate marker of metabolic correction in the brain) to normal or supra-normal levels is consistent with results seen in patients treated with the fresh formulation at the same timepoints.
- The emerging safety profile of the cryopreserved formulation is consistent with the safety profile observed in the fresh formulation. No treatment related adverse events or signs of oncogenic transformation have been reported in the patients receiving the cryopreserved formulation as of the date of the analysis.
- Preliminary evidence also suggests that the first patient treated with the cryopreserved formulation has acquired motor capabilities consistent with the physiologically progressive acquisition of new motor skills observed in healthy children. At the time of the 12-month assessment, the patient had surpassed the expected age of disease onset (15 months) based on an older untreated sibling, while attaining age-appropriate motor development.

Figure 1. Profiles of VCN in bone marrow $CD34^+$ cells: OTL-200 cryopreserved vs. OTL-200 fresh

https://www.globenewswire.com/NewsRoom/AttachmentNg/83f41457-927b-4b1b-9ac2-9d48ac10353a

Figure 2. ARSA activity profile in peripheral blood: OTL-200 cryopreserved vs. OTL-200 fresh

https://www.globenewswire.com/NewsRoom/AttachmentNg/393ca5f0-98ad-47f8-b723-35c5c6c08d8f

c = cryopreserved; f = fresh; Sbj. = subject

“We are pleased that these initial data suggest that using gene-corrected cells that have been cryopreserved has a similar impact on clinical biomarkers for early-onset MLD patients as the OTL-200 fresh formulation,” said Dr. Valeria Calbi, a hematologist at San Raffaele Scientific Institute and SR-Tiget and an investigator of the study. “The four treated patients showed good levels of engraftment of gene-corrected cells and reconstitution of ARSA activity at multiple time points, as well as encouraging early trends in GMFM scores that we look forward to evaluating with additional follow-up. We believe that these data further support the positive benefit / risk profile of OTL-200 as a therapy with potential lifelong benefit for patients with MLD.”

Next Steps for OTL-200
Orchard remains on track to submit a marketing authorization application, or MAA, in Europe for MLD in the first half of 2020, as well as a biologics licensing application, or BLA, in the U.S. approximately one year later.

About MLD and OTL-200
Metachromatic leukodystrophy (MLD) is a rare and life-threatening inherited disease of the body’s metabolic system occurring in approximately one in every 100,000 live births. MLD is caused by a mutation in the arylsulfatase-A (ARSA) gene that results in the accumulation of sulfatides in the brain and other areas of the body, including the liver, the gallbladder, kidneys, and/or spleen. Over time, the nervous system is damaged and patients with MLD will experience neurological problems such as motor, behavioral and cognitive regression, severe spasticity and seizures, finding it more and more difficult to move, talk, swallow, eat and see. Currently, there are no effective treatments for MLD. In its late infantile form, mortality at 5 years from onset is estimated at 50% and 44% at 10 years for juvenile patients.[1] OTL-200 is an *ex vivo*, autologous, hematopoietic stem cell-based gene therapy

being studied for the treatment of MLD. OTL-200 was acquired from GSK in April 2018 and originated from a pioneering collaboration between GSK and the Hospital San Raffaele and Fondazione Telethon, acting through their joint San Raffaele-Telethon Institute for Gene Therapy in Milan, initiated in 2010.

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 U.K. and the U.S., including London, San Francisco and Boston.

Forward-Looking Statements
This press release contains certain forward-looking statements 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, Orchard's expectations regarding the timing of regulatory submissions for approval of its product candidates, including OTL-200 for the treatment of metachromatic leukodystrophy, the timing of interactions with regulators and regulatory submissions related to ongoing and new clinical trials for its product candidates, the timing of announcement of clinical data for its product candidates, including OTL-200, and the likelihood that such data will be positive and support further clinical development and regulatory approval of its 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 OTL-200, 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]Mahmood et al. Metachromatic Leukodystrophy: A Case of Triplets with the Late Infantile Variant and a Systematic Review of the Literature. Journal of Child Neurology 2010, DOI: http://doi.org/10.1177/0883073809341669

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Source: Orchard Therapeutics (Europe) Limited