Orchard Therapeutics Announces Presentation of Updated Integrated Analysis of OTL-200 in MLD and Reports Progress with Newborn Screening Efforts at the 19th Annual WORLDSymposium™

February 24, 2023

Administration of one-time gene therapy resulted in statistically significant improvement in severe motor impairment-free survival with up to 11 years of follow-up (median 6.15 years)

Composite primary endpoint used in analysis was developed through ongoing discussions with the U.S. Food and Drug Administration and has been agreed to as clinically meaningful

Three genetically confirmed cases of MLD following screening of 96,000 newborns globally to date

BOSTON and LONDON, Feb. 24, 2023 (GLOBE NEWSWIRE) -- Orchard Therapeutics (Nasdaq: ORTX), a global gene therapy leader, today announced long-term results from an updated integrated analysis of 39 patients with metachromatic leukodystrophy (MLD) treated with investigational OTL-200 in the clinical development program. The data are being presented at the ongoing 19th Annual WORLD*Symposium*™ taking place February 22-26, 2023, in Orlando, Florida.

"MLD is a devastating and ultimately fatal disease that robs children of the ability to walk, talk and engage with the world around them," said Dr. Francesca Fumagalli, a consulting neurologist at the San Raffaele Telethon Institute for Gene Therapy (SR-Tiget) and Ospedale San Raffaele, and the presenting author of the updated integrated analysis. "In its most severe form, untreated patients typically pass away within five years of symptom onset. These data, which now encompass more than 10 years of follow up in the earliest treated patients, represent a significant step forward in the treatment of MLD and highlight the potential long-term benefits of HSC gene therapy for these children and their families."

Thirty-nine pediatric patients with early-onset MLD, enrolled in two prospective non-randomized clinical studies (n=30) or treated under expanded access frameworks (n=9), were administered OTL-200 and compared with natural history data from 48 untreated patients. All treated patients were administered OTL-200 and subsequently monitored at Ospedale San Raffaele in Milan, Italy.

"These are compelling results that add to the compendium of evidence underscoring the potential of our HSC gene therapy approach to end the devastation caused by severe genetic diseases with a single treatment," said Bobby Gaspar, M.D., Ph.D., chief executive officer of Orchard Therapeutics. "Importantly, the primary endpoint of severe motor impairment-free survival utilized in this updated integrated analysis was developed through our ongoing discussions with the U.S. Food and Drug Administration and has been agreed to as clinically meaningful. We look forward to continuing working with the agency on leveraging these expanded clinical results to support a potential approval of OTL-200 in the U.S."

At the time of the updated integrated analyses (median follow-up 6.15 years, range 0.64-11.03 years), results from treated patients showed:

Efficacy

- Treatment with OTL-200 resulted in statistically significant and clinically meaningful improvement in severe motor impairment-free survival in the pre-symptomatic late infantile (p=<0.001) and early juvenile (p=0.049) and early symptomatic early juvenile (p=<0.001) MLD subgroups compared to disease natural history.
    - Seventeen of 18 pre-symptomatic late infantile patients maintained the ability to walk at last assessment (Gross Motor Function Classification-MLD [GMFC-MLD] Level 2 or better; range of age at last assessment: 1.6 to 12.1 years), in contrast to untreated late infantile natural history patients who lost all locomotion (entry into GMFC-MLD Level 5) by a median age of 2.6 years.
    - All seven surviving pre-symptomatic early juvenile patients maintain the ability to walk without support with quality and performance normal for age at last assessment (GMFC-MLD Level 0; range of age at last assessment: 3.6 to 11.0 years), and seven of nine surviving early-symptomatic early juvenile patients maintained the ability to sit without support and/or crawl/roll at last assessment (GMFC-MLD Level 4 or better; range of age at last assessment: 4.6 to 19.1 years), in contrast with untreated early juvenile natural history patients who lost all locomotion (entry to GMFC-MLD Level 5) by a median age of 6.4 years.
- Seventeen of 18 pre-symptomatic late infantile, all seven surviving pre-symptomatic early juvenile, and eight of nine surviving early-symptomatic early juvenile patients have continued to acquire cognitive skills as expected for age, shown by the upward trajectory of performance and verbal age-equivalents over chronological ages.

- All treated patients had reconstituted ARSA activity in peripheral blood mononuclear cells (PBMCs) with geometric mean values within or above normal range by three months post-treatment and in cerebrospinal fluid by three to 12 months post-treatment, which was sustained throughout follow-up.

Safety

- With a cumulative 232 patient-years of follow-up, treatment with OTL-200 was generally well-tolerated, with no treatment-related serious adverse events or deaths. Most adverse events were associated with busulfan conditioning or background disease. The three patient deaths were considered unrelated to treatment with OTL-200.
- There were six treatment-related adverse events of anti-ARSA antibodies reported, which resolved either spontaneously or after B-cell depleting therapy with no impact on clinical outcome. Antibody titers in all cases were generally low and no negative effects were observed in the engraftment of gene-corrected cells or in post-treatment ARSA activity.
- Delayed platelet engraftment occurred in four patients all of which resolved within the first four months after conditioning with no bleeding events reported. One patient with a complex medical history and comorbidities experienced prolonged anemia and thrombocytopenia requiring infusion of unmanipulated back-up cells and remains in good clinical condition.
- There have been no cases of malignancy or insertional oncogenesis and no evidence of clonal dominance or expansion reported to date, consistent with other Orchard lentiviral HSC gene therapy studies.

Summary of Additional WORLD*Symposium*™ Data Presentations
In total, four oral presentations and 11 posters from across the company's neurometabolic portfolio are being featured at the 19th Annual WORLD*Symposium*™.

In addition to the updated integrated analysis, there are multiple presentations highlighting various newborn screening efforts to support the timely and accurate diagnosis of MLD. To date, there have been three genetically confirmed cases of MLD after screening of 96,000 newborns globally. One of these cases has been assessed clinically and referred for treatment with Libmeldy® (atidarsagene autotemcel) with the other two more recently identified patients pending clinical assessment.

Furthermore, there are several investigator-initiated presentations detailing results of patients treated with OTL-200 in Europe, the U.S. and South America on compassionate use basis with drug product supplied from a European commercial manufacturer, demonstrating the potential for global supply from a centralized cGMP manufacturing site, as well as an encore clinical data presentation from the company's investigational hematopoietic stem cell (HSC) gene therapy OTL-201 for MPS-IIIA.

About MLD
MLD is a rare and life-threatening inherited disease of the body's metabolic system estimated to occur in approximately one in every 100,000 live births based on existing literature. 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, gallbladder, kidneys, and/or spleen. Over time, the nervous system is damaged, leading to neurological problems such as motor, behavioral and cognitive regression, severe spasticity and seizures. Patients with MLD gradually lose the ability to move, talk, swallow, eat and see. In its late infantile form, mortality at five years from onset is estimated at 50 percent and 44 percent at 10 years for juvenile patients.[i]

About Libmeldy / OTL-200
Libmeldy (atidarsagene autotemcel), also known as OTL-200, has been approved by the European Commission for the treatment of metachromatic leukodystrophy (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 of Libmeldy, 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 U.S.

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

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 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, 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, the likelihood that further data will be positive or that MLD screen positive cases will be confirmed clinically. 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, including signals of safety and efficacy, will not be replicated or will not continue in ongoing or future studies and the risk that long-term adverse safety findings may be discovered. 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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[i] *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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