



Orchard Therapeutics Announces Presentation of Data Comprising the Clinical Package for the OTL-200 BLA in MLD at the SSIEM Annual Symposium 2023

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Administration of one-time gene therapy resulted in statistically significant improvement in severe motor impairment-free survival with up to 12 years of follow-up (median 6.76 years)

Composite primary endpoint used in analysis was developed through discussions with the U.S. Food and Drug Administration

Extended follow-up continues to demonstrate sustained preservation of cognitive function and motor development in most patients

BOSTON and LONDON, Aug. 31, 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 were presented yesterday at the ongoing Society for the Study of Inborn Errors of Metabolism (SSIEM) Annual Symposium in Jerusalem.

"MLD is a devastating and ultimately fatal disease for which there are no alternative treatment options beyond supportive care," said Leslie Meltzer, Ph.D., chief medical officer of Orchard Therapeutics. "These data, which now encompass more than a cumulative 250 years of patient experience, continue to show sustained preservation of cognitive function and motor development in most patients compared to disease natural history consistent with previously published results. Moreover, results from the updated integrated analysis presented at SSIEM are key components of the clinical package in the OTL-200 BLA we recently submitted to the FDA."

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 49 untreated patients. All treated patients were administered OTL-200 and subsequently monitored at Ospedale San Raffaele in Milan, Italy.

The composite endpoint used in the updated integrated analysis is severe motor impairment-free survival (sMFS), defined as the interval from birth to the first occurrence of loss of locomotion and loss of sitting without support (Gross Motor Function Classification-MLD [GMFC-MLD] Level \geq 5) or death.

Importantly, use of sMFS was discussed with the U.S. Food and Drug Administration (FDA) who agreed it is clinically meaningful.

At the time of the updated integrated analysis (median follow-up 6.76 years, range 0.64-12.19 years), results from treated patients showed:

Efficacy

- Treatment with OTL-200 resulted in statistically significant and clinically meaningful improvement in sMFS in the pre-symptomatic late infantile ($p < 0.001$), pre-symptomatic early juvenile ($p = 0.042$) 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 (GMFC-MLD Level 2 or better; range of age at last assessment: 3.2 to 13.4 years), in contrast to untreated late infantile natural history patients, all of whom lost all locomotion (GMFC-MLD Level 5 or worse) by a median age of 2.6 years.
 - All seven surviving pre-symptomatic early juvenile patients maintained 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: 2.1 to 11.9 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: 5.1 to 19.1 years), in contrast with untreated early juvenile natural history patients, all of whom lost all locomotion (GMFC-MLD Level 5 or worse) by a median age of 6.4 years.
- Seventeen of 18 pre-symptomatic late infantile, all seven surviving pre-symptomatic early juvenile, and six 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 six months post-treatment, which has been sustained throughout follow-up.

Safety

- With more than a cumulative 250 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. There were three patient deaths observed in the study, none of which were considered related to treatment with OTL-200.
- 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.

As previously [announced](#), the company has completed the rolling submission of its Biologics License Application (BLA) to the U.S. Food and Drug Administration (FDA) for OTL-200, in children with early-onset MLD. OTL-200 previously received both Rare Pediatric Disease (RPD) and Regenerative Medicine Advanced Therapy (RMAT) designations from the FDA. Orchard Therapeutics has requested priority review, which if granted, would put OTL-200 on track for a potential U.S. approval in the first half of 2024.

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.¹

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 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. 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.

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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