



## Orchard Therapeutics Announces Publication in *The Lancet* of Long-term Clinical Outcomes with Libmeldy for the Treatment of Children with Early-onset MLD

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*Administration of one-time hematopoietic stem cell (HSC) gene therapy resulted in sustained, clinically meaningful benefits by preserving cognitive function and motor development in most patients*

*90% overall survival with up to 7.5 years of follow-up (median 3.2 years) in 29 patients*

BOSTON and LONDON, Jan. 21, 2022 (GLOBE NEWSWIRE) -- Orchard Therapeutics (Nasdaq: ORTX), a global gene therapy leader, today announced the publication in *The Lancet* of long-term clinical outcomes evaluating the safety and efficacy of Libmeldy® (atidarsagene autotemcel) for the treatment of early-onset metachromatic leukodystrophy (MLD). Libmeldy is the only approved one-time gene therapy intended to correct the underlying cause of MLD for eligible patients in the European Union, UK, Iceland, Liechtenstein and Norway. Also known as OTL-200, it is an investigational therapy in the U.S.

"MLD is a cruel and ultimately fatal disease for which there were previously no approved treatment options beyond supportive care," said Professor Alessandro Aiuti, deputy director of the San Raffaele Telethon Institute for Gene Therapy in Milan and full professor of pediatrics at the Vita-Salute San Raffaele University of Milan and a senior author of *The Lancet* manuscript. "Libmeldy represents a significant step forward in the treatment of MLD. These data highlight the potential long-term benefits of HSC gene therapy for these children, especially when intervention prior to symptom onset is possible."

Twenty-nine pediatric patients with early-onset MLD, enrolled in either a prospective non-randomized clinical study (n=20) or treated under expanded access frameworks (n=9), were administered Libmeldy and compared with an untreated natural history cohort of 31 patients adjusted for age and disease subtype. Most patients treated with Libmeldy developed motor skills within the predicted range of healthy children or maintained the ability to walk. Treatment with Libmeldy was well-tolerated and there was no evidence of abnormal clonal proliferation or replication-competent lentivirus over the follow up period. There were no treatment-related mortality or serious adverse events. Most adverse events were related to conditioning or background disease. Four patients developed transient anti-ARSA antibodies, which did not impact clinical outcomes.

"Treatment with Libmeldy resulted in sustained, clinically relevant benefits in children with early-onset MLD by preserving motor development and cognitive function in most patients," said Bobby Gaspar, M.D., Ph.D., chief executive officer of Orchard Therapeutics. "These are compelling results that underscore the potential of our HSC gene therapy approach to end the devastation caused by severe genetic diseases with a single treatment. We are commercializing Libmeldy in Europe and intend to pursue future potential regulatory approvals."

### Summary of Results Published in *The Lancet*

An integrated analysis was performed on data from 29 pediatric patients with a molecular and biochemical diagnosis of MLD and with either pre-symptomatic late-infantile (typically ranging from six to 30 months old at symptom onset) or pre- or early-symptomatic early juvenile (typically between 30 months and less than seven years old at symptom onset) disease and treated with Libmeldy in a prospective non-randomized clinical study or under expanded access frameworks. These included 16 (55%) pre-symptomatic late-infantile patients (one pre-symptomatic at enrollment became symptomatic by the time of treatment) and 13 (45%) early juvenile patients, eight of whom were early-symptomatic at the time of treatment. Patients were treated and monitored at Ospedale San Raffaele, Milan, Italy. Treated patients were compared with a historical cohort of 31 age- and disease subtype-matched MLD patients from a non-interventional natural history study.

At the time of analyses in 2018, results from all treated patients showed:

#### *Efficacy Results*

- Total gross motor function measure (GMFM) scores were significantly improved in Libmeldy-treated patients compared to the natural history cohort at two years post-treatment (co-primary endpoint) for both late-infantile (66 percentage points [95% Confidence Interval (CI) 48.9–82.3],  $p < 0.0001$ ) and early juvenile patients (42 percentage points [95% CI 12.3–71.8],  $p = 0.036$ ). The difference was even larger at three years and remained statistically significant for both late-infantile and early juvenile patients.
- Most treated patients displayed normal cognitive development, as well as prevention or delay of central and peripheral demyelination and brain atrophy throughout follow-up. Treatment benefits were particularly apparent in patients treated before symptom onset.

- All treated patients had reconstituted ARSA activity in peripheral blood mononuclear cells (PBMCs) within or above normal range from three months post-treatment and onward with levels significantly increased above baseline at two years post-treatment (co-primary endpoint).
- Twenty-six of 29 patients (90%) were alive with median follow-up of 3.2 years (range 0.64 to 7.51 years) in all participants. Of the three deaths which occurred during the follow-up period, two were due to rapid disease progression in early symptomatic early juvenile patients (8- and 15-months post-treatment, respectively) and were considered unrelated to treatment. The third death was due to ischemic stroke following an infectious event 13.6 months post-treatment in a pre-symptomatic early juvenile patient, which was also determined by study investigators as unlikely related to treatment.

#### *Safety Data*

- Treatment with Libmeldy was well-tolerated, with no treatment-related serious adverse events. Most adverse events were associated with busulfan conditioning or background disease. The most frequently reported grade  $\geq 3$  AEs were febrile neutropenia (n=23, 79%), gait disturbance (n=15, 52%), and stomatitis (n=12, 41%).
- Five treatment-related events of anti-ARSA antibodies were reported in four (14%) of patients, which resolved spontaneously or after B-cell depleting therapy, with no obvious impact on clinical outcome or safety profile. 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.

#### **About MLD**

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, 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.<sup>1</sup>

#### **About Libmeldy / OTL-200**

Libmeldy (atidarsagene autotemcel), also known as OTL-200, has been approved by the European Commission for the treatment of 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, 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 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 has a deep 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](http://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](http://www.orchard-tx.com)), the investor relations website ([ir.orchard-tx.com](http://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 and these channels, and 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 "intends," "possible," "believes," "expects," "projects," and "potential" 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 safety and efficacy of Libmeldy and 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 prior results, such as signals of safety, activity or durability of effect, observed from clinical trials of Libmeldy will not continue or be repeated in our ongoing or planned clinical trials of Libmeldy, will be insufficient to maintain marketing approval in the EU, or that long-term adverse safety findings may be discovered; the risk that Orchard may not secure adequate pricing or reimbursement to support continued development or commercialization of Libmeldy; the risk that the market opportunity for Libmeldy may be lower than estimated; and the risk that OTL-200 will not obtain marketing approval in the U.S. 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, 2021, 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.

<sup>i</sup> *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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