Orchard Therapeutics Receives Positive CHMP Opinion for Libmeldy™ for the Treatment of Early-Onset Metachromatic Leukodystrophy (MLD)

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First therapy recommended for full marketing authorization in the EU for eligible patients with confirmed diagnosis of late infantile or early juvenile MLD variants

One-time treatment with Libmeldy has been shown to preserve cognitive and motor function in most patients

Libmeldy is backed by data across 35 patients with follow-up of up to 8 years post-treatment, demonstrating the potential durability of HSC gene therapy

BOSTON and LONDON, Oct. 16, 2020 (GLOBE NEWSWIRE) -- Orchard Therapeutics (Nasdaq: ORTX), a global gene therapy leader, today announced that the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) has adopted a positive opinion recommending full, or standard, marketing authorization for Libmeldy (cryopreserved autologous CD34+ cells encoding the *arylsulfatase-A*, or *ARSA*, gene), an investigational gene therapy for the treatment of metachromatic leukodystrophy (MLD), 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.

The CHMP's positive opinion will now be reviewed by the European Commission (EC), which has the authority to grant marketing authorization for Libmeldy in the European Union (EU). A final decision by the EC for Libmeldy is anticipated before the end of 2020. If approved, Libmeldy would be the first commercial therapy and first gene therapy for eligible patients with early-onset MLD.

MLD is a very rare, severe genetic condition caused by mutations in the *ARSA* gene which lead to neurological damage and developmental regression. In its most severe and common forms, young children rapidly lose the ability to walk, talk and interact with the world around them. A majority of these patients pass away in childhood, with palliative care often as their only option.

"Today's positive CHMP opinion for marketing authorization of Libmeldy is a remarkable achievement that we share with the MLD community, as it brings us closer to delivering a one-time, potentially transformative therapy for eligible children suffering from this devastating disease," said Bobby Gaspar, M.D., Ph.D., chief executive officer, Orchard Therapeutics. "Data from the Libmeldy clinical program have demonstrated the potential for long-term positive effects on cognitive development and maintenance of motor function, translating to individual preservation of motor milestones such as the ability to sit, stand and/or walk without support, as well as attainment of cognitive skills like social interactions and school attendance, at ages at which untreated patients show severe motor and cognitive impairments."

Libmeldy is designed as a one-time gene therapy, developed in partnership with the San Raffaele-Telethon Institute for Gene Therapy (SR-Tiget) in Milan, Italy, in which the patient's own hematopoietic stem cells (HSCs) are selected, and functional copies of the *ARSA* gene are inserted into the genome of the HSCs using a lentiviral vector before these genetically modified cells are infused back into the patient. The ability of the gene-corrected HSCs to migrate across the blood-brain barrier into the brain, engraft, and express the functional enzyme has the potential to persistently correct the underlying genetic condition with a single treatment.

"This is an important milestone toward making the availability of HSC gene therapy a reality for more patients, and it also is extremely rewarding for our multi-disciplinary team at SR-Tiget who has worked relentlessly along this 15-year journey to move the seminal proof of principle studies to the first in-human testing of this therapy," said SR-Tiget director Luigi Naldini, M.D, Ph.D. "The robust and durable clinical benefits observed in early-onset MLD patients who received HSC gene therapy are compelling, especially when compared to the natural history of the disease. These results also further illustrate our view that the HSC gene therapy approach has the potential to deliver transformative effects in other storage diseases as well, especially when the cells are designed to overexpress the functional enzyme and provide an enhanced supply of it to the affected tissues."

"As a parent, watching your child start down a seemingly normal developmental path only to suddenly and rapidly lose some or all of his or her abilities is heart-wrenching, and the agony is even more acute knowing no approved therapies currently exist for MLD," said Georgina Morton, Chair of ArchAngel MLD Trust. "Today's decision to advance Libmeldy to the final EC approval stage represents a huge step forward for the parents of these young children and for all of us in the MLD community."

"We are extremely appreciative of the EMA's expedited and thorough review of Libmeldy's marketing authorization application, considering the severity of MLD coupled with the limited treatment options available today for young patients," said Anne Dupraz, chief regulatory officer, Orchard Therapeutics. "The Agency's collaboration on this assessment is a testament to their broader public health commitment to ensure timely evaluation of new medicines for diseases where a pressing unmet need exists."

Data Supporting the Clinical Profile of Libmeldy

The positive CHMP opinion is supported by clinical studies of Libmeldy in both pre- and early- symptomatic, early-onset MLD patients. Early-onset MLD encompasses the disease variants traditionally referred to as late infantile (LI) and early juvenile (EJ).

Clinical efficacy was based on the integrated analysis of results from 29 patients with early-onset MLD who were all treated with Libmeldy prepared as a fresh (non-cryopreserved) formulation:

- 20 patients were treated in a registrational study (median 4 years follow-up); 9 patients were treated in expanded access programs (median 1.5 years follow-up).
- 16 patients had a diagnosis of LI MLD; 13 had a diagnosis of EJ MLD.
- At the time of treatment, 20 patients were deemed pre-symptomatic; 9 were deemed early-symptomatic.

Clinical safety was evaluated in 35 patients with early-onset MLD:

- 29 patients from integrated efficacy analysis (above).
- 6 patients treated with the cryopreserved formulation of Libmeldy.

Co-primary endpoints
The co-primary endpoints of the integrated efficacy analysis were Gross Motor Function Measure (GMFM) total score and ARSA activity, both evaluated at 2 years post-treatment. Results of this analysis indicate that a single-dose intravenous administration of Libmeldy is effective in modifying the disease course of early-onset MLD in most patients.

Pre-symptomatic LI and EJ patients treated with Libmeldy experienced significantly less deterioration in motor function at 2 years and 3 years post-treatment, as measured by GMFM total score, compared to age and disease subtype-matched untreated patients ($p \leq 0.008$). The mean difference between treated pre-symptomatic LI patients and age-matched untreated LI patients was 71.0% at year 2 and 79.8% at year 3. Similarly, the mean difference between treated pre-symptomatic EJ patients and age-matched untreated EJ patients was 52.4% at year 2 and 74.9% at year 3. Although not statistically significant, a clear difference in GMFM total score was also noted between treated early-symptomatic EJ patients and age-matched untreated EJ patients (28.7% at year 2; $p=0.350$ and 43.9% at year 3; $p=0.054$).

A statistically significant increase in ARSA activity in peripheral blood mononuclear cells was observed at 2 years post-treatment compared to pre-treatment in both pre-symptomatic patients (20.0-fold increase; $p<0.001$) and early-symptomatic patients (4.2-fold increase; $p=0.004$).

At the time of the integrated data analysis, all treated LI patients were alive with a follow-up post-treatment up to 7.5 years and 10 out of 13 treated EJ patients were alive with a follow-up post-treatment of up to 6.5 years. No treatment-related mortality has been reported in patients treated with Libmeldy.

Key secondary endpoints
For EJ patients who were early-symptomatic when treated with Libmeldy, meaningful effects on motor development were demonstrated when these patients were treated before entering the rapidly progressive phase of the disease (IQ≥85 and Gross Motor Function Classification (GMFC)≤1). By 4 years post-disease onset, an estimated 62.5% of treated, early-symptomatic EJ MLD patients survived and maintained locomotion and ability to sit without support compared with 26.3% of untreated early-symptomatic EJ MLD patients, representing a delay in disease progression following treatment with Libmeldy.

A secondary efficacy endpoint that measured cognitive and language abilities as quantified by Intelligence Quotient/Development Quotient (IQ/DQ) found:

- In the treated LI subgroup:
  - 12 out of 15 assessed patients had a fairly constant IQ/DQ, within the normal range (IQ/DQ score of 100 +/- SD of 15) throughout follow-up.
  - All but 2 of these patients (1 pre-symptomatic and 1 early-symptomatic) remained above the threshold of severe mental disability (IQ/DQ>55) at chronological ages at which all 14 untreated comparator LI patients showed evidence of severe cognitive impairment (i.e. IQ/DQ below 55 and close to 0).
- Of the 10 surviving EJ patients:
  - All 4 pre-symptomatic patients and 4 out of 6 early-symptomatic patients showed normal IQ/DQ throughout follow-up. In contrast, 11 out of 12 untreated EJ patients showed evidence of severe cognitive impairment during follow-up.

Clinical safety
Safety data indicate that Libmeldy was generally well-tolerated. The most common adverse reaction attributed to treatment with Libmeldy was the occurrence of anti-ARSA antibodies (AAA) reported in 5 out of 35 patients. Antibody titers in all 5 patients were generally low and no negative effects were observed in post-treatment ARSA activity in the peripheral blood or bone marrow cellular subpopulations, nor in the ARSA activity within the cerebrospinal fluid. 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.

About MLD and Investigational Libmeldy

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, 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. Currently, there are no approved 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] Libmeldy (autologous CD34+ cell enriched population that contains hematopoietic stem and progenitor cells (HSPC) transduced *ex vivo* using a lentiviral vector encoding the human *arylsulfatase-A* (*ARSA*) gene), formerly OTL-200, is being studied for the treatment of MLD in certain patients. Libmeldy 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 global gene therapy leader dedicated to transforming the lives of people affected by rare diseases through the development of innovative, potentially curative gene therapies. Our *ex vivo* autologous gene therapy approach harnesses the power of genetically modified blood stem cells and seeks to correct the underlying cause of disease in a single administration. In 2018, Orchard 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. Orchard now has one of the deepest and most advanced gene therapy product candidate pipelines in the industry spanning multiple therapeutic areas where the disease burden on children, families and caregivers is immense 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 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," "plans," "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 business strategy and goals, including its plans and expectations for the regulatory approval and commercialization of Libmeldy, and the therapeutic potential of Libmeldy, including the potential implications of clinical data for eligible patients. 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 our marketing authorization application submitted for Libmeldy may not be approved by the European Commission when expected, or at all; 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 support regulatory submissions or marketing approval in the US and EU or that long-term adverse safety findings may be discovered; the inability or risk of delays in Orchard's ability to commercialize Libmeldy, if approved, including the risk that we may not secure adequate pricing or reimbursement to support continued development or commercialization of Libmeldy; and the severity of the impact of the COVID-19 pandemic on Orchard's business, including on clinical development, its supply chain and commercial programs. 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 June 30, 2020, 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.

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[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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