

Orchard Therapeutics Receives EC Approval for Libmeldy™ for the Treatment of Early-Onset Metachromatic Leukodystrophy (MLD)

First gene therapy to receive full EU marketing authorization for eligible MLD patients

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

Achievement shared with research alliance partners Fondazione Telethon and Ospedale San Raffaele

BOSTON/LONDON/MILAN, December 21, 2020 – Orchard Therapeutics (Nasdaq: ORTX), a global gene therapy leader, and its research alliance partners Fondazione Telethon and Ospedale San Raffaele, today announced that the European Commission (EC) granted full (standard) market authorization for Libmeldy (autologous CD34+ cells encoding the *ARSA* gene), a lentiviral vector-based gene therapy approved 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. Libmeldy is the first therapy approved for eligible patients with early-onset MLD.

MLD is a very rare, fatal genetic disorder 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, and most pass away before adolescence. Libmeldy is designed as a one-time therapy that aims to correct the underlying genetic cause of MLD, offering eligible young patients the potential for long-term positive effects on cognitive development and maintenance of motor function at ages at which untreated patients show severe motor and cognitive impairments.

“Today’s EC approval of Libmeldy opens up tremendous new possibilities for eligible MLD children faced with this devastating disease where previously no approved treatment options existed,” said Bobby Gaspar, M.D., Ph.D., chief executive officer of Orchard. “Libmeldy is Orchard’s first product approval as a company, and I am extremely proud of the entire team who helped achieve this milestone. We are grateful for and humbled by the opportunity to bring this remarkable innovation to young eligible patients in the EU.”

With Libmeldy, a 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 self-inactivating (SIN) 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 disease with a single treatment.

“The EC approval of Libmeldy comes more than a decade after the first patient was treated in clinical trials performed at our Institute, and ushers in a remarkable and long-awaited shift in the treatment landscape for eligible MLD patients, said Luigi Naldini, M.D, Ph.D., director of the San Raffaele-Telethon Institute for Gene Therapy (SR-Tiget) in Milan, Italy. “Our team at SR-Tiget has been instrumental in advancing the discovery and early-stage research of this potentially transformative therapy to clinical trials in support of its registration through more than 15 years of studies supported by Fondazione Telethon and Ospedale San Raffaele, and we are

extremely proud of this achievement and what it means for patients and the field of HSC gene therapy.”

“MLD is a heart-breaking disease that causes immeasurable suffering and robs children of the chance of life,” said Georgina Morton, chairperson of ArchAngel MLD Trust. “As a community, we have been desperate for a treatment for young MLD patients, and we are incredibly excited to now have such a ground-breaking option approved in the EU.”

The marketing authorization for Libmeldy is valid in all 27 member states of the EU as well as the UK, Iceland, Liechtenstein and Norway. Orchard is currently undertaking EU launch preparations related to commercial drug manufacturing, treatment site qualification and market access.

Data Supporting the Clinical and Safety Profile of Libmeldy

The marketing authorization for Libmeldy is supported by clinical studies in both pre- and early-symptomatic, early-onset MLD patients performed at the SR-Tiget. Early-onset MLD encompasses the disease variants often referred to as late infantile (LI) and early juvenile (EJ). Clinical efficacy was based on the integrated data analysis from 29 patients with early-onset MLD who were treated with Libmeldy prepared as a fresh (non-cryopreserved) formulation. 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.

Clinical safety was evaluated in 35 patients with MLD (the 29 patients from the integrated efficacy analysis as well as six additional patients treated with the cryopreserved formulation of Libmeldy). 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 five out of 35 patients. Antibody titers in all five 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. 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 further details, please see the Summary of Product Characteristics (SmPC).

About MLD and Libmeldy

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% and 44% at 10 years for juvenile patients.ⁱ

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), also known as OTL-200, is approved in the European Union for the treatment of MLD in eligible early-onset patients. In the U.S., OTL-200 is an investigational therapy which has not been approved by the U.S. Food and Drug Administration (FDA) for any use. 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.

About Fondazione Telethon, Ospedale San Raffaele and the San Raffaele-Telethon Institute for Gene Therapy (SR-Tiget)

Based in Milan, Italy, the San Raffaele-Telethon Institute for Gene Therapy (SR-Tiget) is a joint venture between the Ospedale San Raffaele, a clinical-research-university hospital established in 1971 to provide international-level specialized care for the most complex and difficult health conditions, and Fondazione Telethon, an Italian biomedical charity born in 1990 and focused on rare genetic diseases. SR-Tiget was established in 1995 to perform research on gene transfer and cell transplantation and translate its results into clinical applications of gene and cell therapies for different genetic diseases. Over the years, the Institute has given a pioneering contribution to the field with relevant discoveries in vector design, gene transfer strategies, stem cell biology, identity and mechanism of action of innate immune cells. SR-Tiget has also

established the resources and framework for translating these advances into novel experimental therapies and has implemented several successful gene therapy clinical trials for inherited immunodeficiencies, blood and storage disorders, which have already treated >115 patients and have led through collaboration with industrial partners to the filing and approval of novel advanced gene therapy medicines.

For more information:

- www.telethon.it/en
- <https://research.hsr.it/en/institutes/san-raffaele-telethon-institute-for-gene-therapy.html>

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 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 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 or to maintain marketing approval in the EU, or that long-term adverse safety findings may be discovered; the inability or risk of delays in Orchard's ability to commercialize Libmeldy, including the risk that we may not secure adequate pricing or reimbursement to support continued development or commercialization of Libmeldy; the risk that the market opportunity for Libmeldy, or any of Orchard's product candidates, may be lower than estimated; 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 September 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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