



Orchard Therapeutics Outlines U.S. Launch Plans for Lenmeldy™ (atidarsagene autotemcel), the Only Approved Therapy for Children with Early-onset Metachromatic Leukodystrophy

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Five specialized treatment centers being qualified across the U.S. to minimize travel burden on eligible patients and their families

Orchard Assist patient services program to provide individualized support throughout the treatment process

Lenmeldy wholesale acquisition cost of \$4.25 million for one-time treatment reflects its clinical, economic and societal value

Innovative outcomes- and value-based agreements are being offered to both private and government insurers to ensure broad, expedient and sustainable reimbursed access

TOKYO, LONDON and BOSTON, March 20, 2024 (GLOBE NEWSWIRE) -- Orchard Therapeutics, recently acquired by Kyowa Kirin with the goal of accelerating the delivery of new gene therapies to patients around the globe, today announced the details of its U.S. commercial launch of Lenmeldy™ (atidarsagene autotemcel), formerly known as OTL-200, the first FDA-approved therapy for the treatment of children with pre-symptomatic late infantile (PSLI), pre-symptomatic early juvenile, (PSEJ), or early symptomatic early juvenile (ESEJ)—collectively referred to as early-onset—metachromatic leukodystrophy (MLD).

MLD is an ultra-rare, rapidly progressive, irreversible and ultimately fatal neurometabolic disease that affects approximately one in 100,000 live births, which is estimated to be fewer than 40 children annually in the U.S. It is caused by a mutation in the gene responsible for encoding the enzyme arylsulfatase A (ARSA) leading to neurological damage and developmental regression. In the most severe form of MLD, babies develop normally but in late infancy start to rapidly lose the ability to walk, talk and interact with the world around them. These children eventually deteriorate into a vegetative state, which may require 24-hour intensive care, and the majority pass away within five years of symptom onset, creating an enormous emotional and financial burden on the family. Prior to Lenmeldy, there were no treatment options in the U.S. for early-onset MLD beyond supportive and end-of-life care.

Lenmeldy aims to correct the underlying genetic cause of MLD by inserting one or more functional copies of the human *ARSA* gene *ex vivo* (outside the body) into the genome of a patient's own hematopoietic stem cells (HSCs) using a lentiviral vector. The genetically repaired cells are infused back into the patient, where, once engrafted, they differentiate into multiple cell types, some of which migrate across the blood-brain barrier into the central nervous system and express the functional enzyme. Prior to treatment, patients must undergo high-dose chemotherapy, a process that removes cells from the bone marrow so they can be replaced with the modified cells in Lenmeldy. This approach has the potential to restore enzymatic function to stop or slow disease progression with a single treatment.

"Lenmeldy is truly a paradigm-shifting medicine and has the potential to stop or slow the progression of this devastating childhood disease with a single treatment, particularly when administered prior to the onset of symptoms," said Bobby Gaspar, M.D., Ph.D., co-founder and chief executive officer of Orchard Therapeutics. "We are committed to enabling broad, expedient and sustainable access to this important therapy for eligible patients with early-onset MLD in the U.S."

"The launch of Lenmeldy in the United States will build on our success delivering personalized gene therapies to eligible children with MLD throughout Europe and the Middle East by utilizing a similar commercial strategy and infrastructure," said Frank Thomas, president and chief operating officer of Orchard Therapeutics. "We are confident in the potential long-term clinical outcomes of Lenmeldy and will continue to work with public and private payers to structure outcomes-based and other types of innovative reimbursement models that appropriately balance the needs of patients and families for adequate access, health care systems for affordability, as well as support future research and development of treatments for ultra-rare diseases like MLD."

Clinical data supporting U.S. approval of Lenmeldy

The FDA approval of Lenmeldy is based on data from 37 pediatric patients with early-onset MLD, enrolled in two single-arm, open-label clinical studies or treated under European expanded access frameworks, who received a one-time administration of the gene therapy and compared with natural history data. All treated patients were administered Lenmeldy and subsequently monitored at Ospedale San Raffaele in Milan, Italy.

All children with PSLI MLD who were treated with Lenmeldy were alive at 6 years of age, compared to only 58% of children in the natural history group. At 5 years of age, 71% of treated children were able to walk without assistance and 85% of the children treated had normal language and performance IQ scores, which has not been reported in untreated children. In addition, children with PSEJ and ESEJ MLD showed slowing of motor and/or cognitive disease.

The most common side effects of Lenmeldy are fever and low white blood cell count, mouth sores, respiratory infections, rash, medical line infections, viral infections, fever, gastrointestinal infections and enlarged liver. After infusion with Lenmeldy, patients should be monitored for neutrophil counts and risk of delayed platelet engraftment until engraftment has been achieved. Treatment with Lenmeldy may be associated with formation of blood clots or a type of swelling of brain tissues known as encephalitis. There is a potential risk of blood cancer associated with this type of treatment; however, no cases have been seen in patients treated with Lenmeldy. Patients receiving this therapy should have life-long monitoring for hematologic malignancies, including a complete blood count (with differential) annually and integration site analysis, as warranted, for at least 15 years after treatment. Please see below for additional details and Important Safety Information.

With more than 12 years of follow-up in the earliest treated patients (median of 6.76 years), Lenmeldy is launching with the longest duration of

follow-up available at the time of approval for a gene therapy in the U.S. to date.

Wholesale acquisition cost reflects potential value of one-time, personalized gene therapies

Orchard Therapeutics has set the wholesale acquisition cost (WAC) of Lenmeldy in the U.S. at \$4.25 million which is reflective of the value the therapy may deliver to eligible patients and their families, as well the potential long-term impact treatment may have on overall healthcare utilization, minimization of productivity loss for caregivers, and life opportunities for patients. The WAC was determined following the completion of a comprehensive Health Technology Assessment (HTA) by the independent, non-profit organization, the Institute for Clinical and Economic Review (ICER) which determined the health benefit price benchmark (HBPB) for Lenmeldy to be up to \$3.94 million at the \$150,000 per Equal Value Life Year (evLY) threshold from a modified societal perspective.

“The value of Lenmeldy has been recognized by several HTA authorities around the world, including in the U.S. by ICER, which determined Lenmeldy to have the highest value-based price for any treatment it has evaluated to date,” said Bennett Smith, senior vice president and general manager of North America at Orchard Therapeutics. “MLD places an enormous emotional and economic burden on families and caregivers—who face substantial wage loss and added expenses each year as the disease progresses—all while dealing with the unquantifiable anguish of losing their child. HSC gene therapy has the potential to offer a transformative impact on devastating genetic diseases not well addressed by other therapeutic modalities, and we will continue to ensure society reaps the benefits from the anticipated value these therapies may deliver to eligible children and their families.”

Enabling timely access and reimbursement

Lenmeldy is launching with an unprecedented amount of follow-up data, providing support for the potential long-term durability of treatment effect. Recognizing the need to establish innovative payment structures for one-time durable therapies, Orchard Therapeutics is working collaboratively with commercial and government payers to offer outcomes- and value-based agreements intended to ensure timely access by sharing risk between the payer and manufacturer.

Finalizing qualification of specialized treatment centers across the U.S.

Lenmeldy is being made available to eligible patients through a network of Qualified Treatment Centers (QTCs) in key regions throughout the United States to minimize the travel burden on patients and their families. Five treatment centers with specialized expertise in transplant and the treatment of neurometabolic diseases, like MLD, are being activated.

One of those centers, the M Health Fairview Masonic Children’s Hospital in Minnesota, is in the final stages of qualification. Several eligible children with MLD from the U.S. have already been treated at the center on a compassionate use basis with drug product supplied by Orchard Therapeutics manufactured using commercial processes.

Four additional regional centers geographically dispersed throughout the United States, including Children’s Healthcare of Atlanta, Children’s Hospital of Philadelphia, Texas Children’s Hospital, and UCSF Benioff Children’s Hospital San Francisco, are in the process of becoming fully qualified.

Supporting patients and their families throughout the treatment process

Orchard Therapeutics’ patient support program, Orchard Assist, will offer individualized support for eligible patients and their caregivers who enroll in the program throughout the treatment process.

Experienced case managers with success supporting patients and their families with both private and public insurance are available to assist in accessing Lenmeldy. For more information, please visit <https://orchardassist.com>.

Expanding newborn screening efforts

As with many rare, life-threatening pediatric diseases, early detection and diagnosis is key to ensuring the best possible outcomes for patients, and Orchard Therapeutics supports efforts to expand newborn screening (NBS) for diseases like MLD which meet Wilson and Jungner criteria.

Currently, ten prospective NBS studies for MLD are active throughout the U.S., Europe and the Middle East, with approximately 275,000 newborns screened to date. The data from these studies provide critical evidence to support applications for universal screening of MLD in the U.S. and around the world.

Utilizing results from such studies, a multi-stakeholder working group is finalizing a nomination to add MLD to the U.S. Recommended Uniform Screening Panel (RUSP), a national guideline for NBS comprising a list of medical conditions for which the federal government recommends all newborns receive screening. States use the RUSP to help them decide which conditions to include in their NBS panels. Based on current timelines and assumptions, Orchard Therapeutics expects the nomination will be submitted in mid-year 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.ⁱ

About Lenmeldy

Lenmeldy™ (atidarsagene autotemcel), formerly known as OTL-200, is the only approved therapy in the U.S. for the treatment of children with pre-symptomatic late infantile (PSLI), pre-symptomatic early juvenile (PSEJ) or early-symptomatic early juvenile (ESEJ) metachromatic leukodystrophy (MLD).

For additional details about Lenmeldy, please refer to the full [Prescribing Information](#).

In Europe, Lenmeldy is known as Libmeldy®[®], where it has been approved by the European Commission (EC), UK Medicines and Healthcare products

Regulatory Agency (MHRA), and Swiss Agency for Therapeutic Products (Swissmedic). For more information about Libmeldy, please see the [Summary of Product Characteristics \(SmPC\)](#) available on the EMA website.

The program was originated by and developed in partnership with the San Raffaele-Telethon Institute for Gene Therapy (SR-Tiget) in Milan, Italy.

INDICATION

LENMELDY™ (atidarsagene autotemcel) is an autologous hematopoietic stem cell-based gene therapy indicated for the treatment of children with pre-symptomatic late infantile (PSLI), pre-symptomatic early juvenile (PSEJ), or early symptomatic early juvenile (ESEJ) metachromatic leukodystrophy (MLD).

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Thrombosis and Thromboembolic Events:

Treatment with LENMELDY may increase the risk of thrombosis and thromboembolic events. A child with PSEJ MLD died after experiencing a left hemisphere cerebral infarction secondary to a thrombotic event in a large blood vessel approximately 1 year after treatment with LENMELDY. Evaluate the risk factors for thrombosis prior to and after LENMELDY infusion according to best clinical practice.

Encephalitis:

Treatment with LENMELDY may increase the risk of encephalitis. A child with ESEJ developed a serious event of encephalitis after treatment with LENMELDY. The etiology of this event is unclear but attribution to LENMELDY cannot be ruled out. Treatment with LENMELDY may trigger a relapsing-remitting pattern of disease progression. No other events related to encephalitis have been reported during the clinical development of LENMELDY. Monitor children for signs or symptoms of encephalitis after LENMELDY treatment.

Serious Infection:

In the period between start of conditioning and within 1 year after LENMELDY treatment, severe Grade 3 infections occurred in 39% of all children (21% bacterial, 5% viral, 5% bacterial and viral or bacterial and fungal, and 8% unspecified). Grade 3 febrile neutropenia developed within 1 month after LENMELDY infusion in 82% of children. In the event of febrile neutropenia, monitor for signs and symptoms of infection and manage with broad-spectrum antibiotics, fluids, and other supportive care as medically indicated. Monitor children for signs and symptoms of infection after myeloablative conditioning and LENMELDY infusion and treat appropriately. Administer prophylactic antimicrobials according to best clinical practice.

Veno-Occlusive Disease:

Three children (8%) treated in clinical trials of LENMELDY developed veno-occlusive disease (VOD) with one Grade 4 SAE and two Grade 3 AEs. None of these three events met Hy's Law criteria. Monitor children for signs and symptoms of VOD including liver function tests in all children during the first month after LENMELDY infusion. Consider prophylaxis for VOD with anti-thrombotic agents based on risk factors for VOD and best clinical practice.

Delayed Platelet Engraftment (DPE):

DPE has been observed with LENMELDY treatment. Bleeding risk is increased prior to platelet engraftment and may continue after engraftment in children with prolonged thrombocytopenia. In clinical trials of LENMELDY, 4 (10%) children had delayed platelet engraftment after day 60 (range day 67-109), with 3 children requiring platelet transfusions until engraftment occurred. Patients should be informed of the risk of bleeding until platelet recovery has been achieved. Monitor patients for thrombocytopenia and bleeding until platelet engraftment and recovery are achieved.

Neutrophil Engraftment Failure:

There is a potential risk of neutrophil engraftment failure after treatment with LENMELDY. Monitor neutrophil counts until engraftment has been achieved. If neutrophil engraftment failure occurs in a child treated with LENMELDY, provide rescue treatment with the unmanipulated back-up collection of CD34⁺ cells.

Insertional Oncogenesis:

There is a potential risk of LVV-mediated insertional oncogenesis after treatment with LENMELDY. Children treated with LENMELDY may develop hematologic malignancies and should be monitored life-long. Monitor for hematologic malignancies with a complete blood count (with differential) annually and integration site analysis as warranted for at least 15 years after treatment with LENMELDY. In the event that a malignancy occurs, contact Orchard Therapeutics at 1-888-878-0185 for reporting and to obtain instructions on collection of samples for testing.

Hypersensitivity Reactions:

The dimethyl sulfoxide (DMSO) in LENMELDY may cause hypersensitivity reactions, including anaphylaxis which is potentially life-threatening and requires immediate intervention. Hypersensitivity including anaphylaxis can occur in children with and without prior exposure to DMSO. Monitor for hypersensitivity reactions during infusion and after infusion.

Anti-Retroviral Use:

Children should not take prophylactic HIV anti-retroviral medications for at least one month prior to mobilization, or for the expected duration of time needed for the elimination of the medications. Anti-retroviral medications may interfere with the manufacturing of LENMELDY. If a child requires antiretrovirals for HIV prophylaxis, initiation of LENMELDY treatment should be delayed until confirmation of a negative test for HIV.

Interference With Serology Testing:

Due to the likelihood of a false-positive test for HIV, children who have received LENMELDY should not be screened for HIV infection using a PCR-based assay.

USE IN SPECIFIC POPULATIONS

Females and Males of Reproductive Potential

Pregnancy Testing

As a precautionary measure, a negative serum pregnancy test must be confirmed prior to the start of mobilization, and reconfirmed prior to conditioning procedures, and before administration of LENMELDY in females of childbearing potential.

Contraception

Consult the Prescribing Information of the mobilization and conditioning agents for information on the need for effective contraception. Males capable of fathering a child and females of childbearing age should use an effective method of contraception from start of mobilization through at least 6 months after administration of LENMELDY.

Infertility

There are no data on the effects of LENMELDY on fertility.

Data are available on the risk of infertility with myeloablative conditioning. In clinical trials of LENMELDY, seven children (50% of females) developed ovarian failure. Advise children of the option to cryopreserve semen or ova before treatment, if appropriate.

For additional safety information, please see the full [Prescribing Information](#).

About Orchard Therapeutics

Orchard Therapeutics, a Kyowa Kirin company, is a global gene therapy leader focused on ending the devastation caused by genetic and other severe diseases 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 with a single treatment.

Founded in 2015, Orchard's roots go back to some of the first research and clinical developments involving HSC gene therapy. Our team has played a central role in the evolution of this technology from a promising scientific idea to a potentially life-transforming reality. Today, Orchard is advancing a pipeline of 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.

For more information, please visit www.orchard-tx.com.

About Kyowa Kirin

Kyowa Kirin aims to discover novel medicines with life-changing value. As a Japan-based Global Specialty Pharmaceutical Company, we have invested in drug discovery and biotechnology innovation for more than 70 years and are currently working to engineer the next generation of antibodies and cell and gene therapies with the potential to help patients affected by a severe or rare disease. A shared commitment to our values, to sustainable growth, and to making people smile unites us across our four regions – Japan, Asia Pacific, North America, and EMEA/International. You can learn more about the business of Kyowa Kirin at www.kyowakirin.com.

¹Mahmood 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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