



Orchard Therapeutics Receives FDA Approval of Lenmeldy™ (atidarsagene autotemcel), the Only Therapy for Eligible Children with Early-onset Metachromatic Leukodystrophy in the U.S.

March 18, 2024

One-time treatment with Lenmeldy has shown the potential to restore enzymatic function to stop or slow disease progression, with up to 12 years of follow-up (median 6.76 years)

TOKYO and LONDON and BOSTON, March 18, 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 U.S. Food and Drug Administration (FDA) has approved Lenmeldy™ (atidarsagene autotemcel), formerly known as OTL-200, 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).

“The FDA approval of Lenmeldy opens up tremendous new possibilities for children in the U.S. with early-onset MLD who previously had no treatment options beyond supportive and end-of-life care,” said Bobby Gaspar, M.D., Ph.D., co-founder and chief executive officer of Orchard Therapeutics. “MLD is a rapidly progressing, life-limiting and ultimately fatal rare disease that has a devastating impact on afflicted children and their families. This achievement is the culmination of decades of research and development in partnership with our academic and clinical collaborators at the San Raffaele-Telethon Institute for Gene Therapy. I want to express my sincere gratitude to the patients and families who participated in our clinical trials as well as to the broader MLD community—we would not be here today without your contributions and support.”

Dr. Gaspar continued, “I am also incredibly proud of the entire team at Orchard for their tireless effort to make this moment possible, and we look forward to ensuring broad and sustainable access to this remarkable innovation for eligible patients in need.”

MLD is a rare, fatal genetic disorder caused by a mutation in the gene responsible for encoding the enzyme arylsulfatase A (ARSA) leading to neurological damage and developmental regression due to the accumulation of fats called sulfatides in the brain and other areas of the body which, when not broken down, damage the central nervous system over time. In its most severe form, 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 disease onset, creating an enormous emotional and financial burden on the family.

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. This approach has the potential to restore enzymatic function to stop or slow disease progression with a single treatment.

“This is a momentous occasion and I commend the FDA for recognizing the clinical impact Lenmeldy has on this cruel disease,” said Barbara Burton, M.D., attending physician, genetics, genomics and metabolism at the Ann & Robert H. Lurie Children’s Hospital of Chicago. “For too long, my colleagues and I have consoled families at their most vulnerable times—usually following an arduous diagnostic odyssey, coping with a dire prognosis and being told there were no treatments, and then having to watch their young child slip away. With this approval, we are now one significant step closer to ensuring future generations of children, families and healthcare professionals no longer need to experience first-hand the terrible manifestations this disease has on untreated patients.”

“As a mother who lost a child to MLD, it is difficult to articulate how much of a watershed moment this is for patients, families and advocates,” said Maria Kefalas, Ph.D., co-founder of the Calliope Joy Foundation and a founding member of Cure MLD. “I, and so many others in our community, have made it our life’s work to end the horror caused by MLD so other families may not have to face the same terrible fate as ours. Today, we are closer than ever to making that vision a reality, but there’s still more work to be done. With the first therapy for this childhood disease now approved, we must act urgently and collaboratively to enable universal newborn screening for MLD in the U.S. so babies with these pathogenic mutations can be diagnosed and referred for appropriate treatment before the onset of symptoms.”

Lenmeldy was granted Priority Review in September 2023. It was previously given both Rare Pediatric Disease (RPD) and Regenerative Medicine Advanced Therapy (RMAT) designations from FDA. In connection with the approval, Orchard Therapeutics received a Priority Review Voucher (PRV), which will be transferred to GSK in accordance with the terms of the original licensing agreement.

Orchard Therapeutics will provide more details about the launch of Lenmeldy in the U.S. through a separate announcement this week.

Overview of Clinical Development Program and Results

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.

With more than 12 years of follow-up in the earliest treated patients (median 6.76 years), treatment with Lenmeldy significantly extended overall survival and resulted in the preservation of motor function and cognitive skills in most late infantile MLD patients past ages at which untreated patients showed severe cognitive and motor impairments. Lenmeldy also resulted in the preservation of motor function and cognitive skills in some early juvenile MLD patients which is not expected when compared to untreated patients.

The most common non-laboratory adverse reactions (incidence $\geq 10\%$) were: febrile neutropenia (85%), stomatitis (77%), respiratory tract infections (54%), rash (33%), device related infections (31%), other viral infections (28%), pyrexia (21%), gastroenteritis (21%), and hepatomegaly (18%). The most common laboratory abnormalities were: elevated D-dimer (67%), neutropenia (28%), and elevated liver enzymes (23%). Please see below for additional details and Important Safety Information.

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 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. It was licensed by Orchard Therapeutics from GSK in 2018.

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. Consider monitoring D-dimer levels after LENMELDY treatment.

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 an anti-thrombotic such as defibrotide or ursodeoxycholic acid 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 lifelong. 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>