Orchard Therapeutics Announces New England Journal of Medicine Publication of Long-term Clinical Outcomes from its HSC Gene Therapy for MLD and Multiple Presentations at ASGCT 2025

May 13, 2025

LENMELDY™ is the first and only disease-modifying intravenous infusion proven to extend life expectancy in pre-symptomatic late infantile (PSLI) patients and mitigate the cognitive and/or physical impact of early-onset MLD

Six accepted abstracts at ASGCT 2025 detail the therapeutic potential of HSC gene therapy to address severe multi-system diseases

TOKYO, LONDON and BOSTON, May 13, 2025 (GLOBE NEWSWIRE) -- Orchard Therapeutics, a Kyowa Kirin company, today announced a publication on long-term safety and efficacy outcomes for Lenmeldy™ (atidarsagene autotemcel) in the treatment of early-onset metachromatic leukodystrophy (MLD). The manuscript, titled, “Long-term effects of atidarsagene autotemcel for metachromatic leukodystrophy” (F. Fumagalli, V. Calbi, A. Aiuti, *et. al.*) was published in the April 24 issue of *NEJM*.

MLD is an ultra-rare, rapidly progressive, irreversible and ultimately fatal neurometabolic disease that affects approximately one in 100,000 live births. It is caused by an error 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. Lenmeldy is the only approved therapy intended to correct the underlying cause of MLD for eligible patients in the United States (U.S.). It is known as Libmeldy® in Europe.

The FDA approval of Lenmeldy is based on data from 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 hematopoietic stem cell (HSC) gene therapy and compared with natural history data from untreated patients. The *NEJM* publication details clinical outcomes of children treated in these studies. All treated patients were administered HSC gene therapy and subsequently monitored at Ospedale San Raffaele in Milan, Italy. The primary endpoint was severe motor impairment-free survival (sMFS), defined as the interval from birth to the first occurrence of loss of locomotion and loss of sitting without support (Gross Motor Function Classification-MLD [GMFC-MLD] Level ≥ 5) or death.

With more than 12 years of follow-up in the earliest treated patients (median 6.76 years) and more than 250 patient 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.

Treatment with Lenmeldy was well-tolerated, with no treatment-related serious adverse events. Most adverse events were associated with busulfan conditioning or background disease. The most common non-laboratory adverse reactions (incidence ≥ 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.

“Lenmeldy represents a significant step forward in the treatment of MLD, a cruel and ultimately fatal disease for which there were previously no approved treatment options beyond supportive and end-of-life care,” said Bobby Gaspar, M.D., Ph.D., chief executive officer of Orchard Therapeutics. “These compelling results, which encompass more than a cumulative 250 years of patient experience, continue to demonstrate the ability of Lenmeldy to preserve motor and cognitive function in eligible children with MLD particularly when treatment is administered prior to the onset of symptoms.”

Dr. Gaspar continued, “These long-term results, coupled with the homogenous, predictable and precipitous decline and eventual death observed in the natural history cohort, underscores the urgent need to enable timely and accurate diagnosis and intervention through the proliferation of universal newborn screening for MLD.”

Summary of Participation at ASGCT 2025

The company also announced six presentations (three oral and three posters) will be featured at the American Society of Gene and Cell Therapy (ASGCT) 28th Annual Meeting taking place May 13-17 in New Orleans.

Featured data include several accepted abstracts and presentations detailing clinical, biochemical and other functional outcomes from across the company’s commercial- and clinical-stage neurometabolic portfolio in metachromatic leukodystrophy (MLD), the Hurler subtype of mucopolysaccharidosis type I (MPS-IH), and mucopolysaccharidosis type IIIA (MPS-IIIA), also known as Sanfilippo syndrome type A.

Company researchers will also present data derived from its efforts to develop an automated manufacturing process for HSC gene therapy production and in developing an HSC gene therapy approach for the treatment of another lysosomal storage disorder.

Finally, Leslie Meltzer, Ph.D., chief medical officer of Orchard Therapeutics, will give an invited talk on Friday, May 16 at 8:00 a.m. CDT, titled "Developing and delivering hematopoietic stem cell gene therapies to patients with rare neurometabolic diseases," which will explore key insights into the development and delivery of one-time treatments for rare neurometabolic diseases and beyond.

Details of the oral presentations are as follows (all times in CDT):

- Title: Lentiviral hematopoietic stem cell gene therapy (atidarsagene autotemcel) for late juvenile metachromatic leukodystrophy (MLD): Interim analysis of a Phase III trial
  Date/Time: Wednesday, May 14 at 2:45 p.m.
  Presenter: Valeria Calbi

- Title: Treatment effect of atidarsagene autotemcel (arsa-cel) in age-matched treated vs. untreated sibling pairs with early-onset metachromatic leukodystrophy (MLD)
  Date/Time: Friday, May 16 at 1:30 p.m.
  Presenter: Valeria Calbi

- Title: Extensive detoxification and favorable effects on systemic clinical outcomes after Hematopoietic Stem Cell Gene Therapy for Mucopolysaccharidosis Type I-Hurler (OTL-203)
  Date/Time: Friday, May 16 at 2:00 p.m.
  Presenter: Giulia Consiglieri

Details of the poster presentations are as follows (all times in CDT):

- Title: Toward the development of an automated manufacturing process for hematopoietic stem cell gene therapies
  Date/Time: Wednesday, May 14 from 5:30 to 7:00 p.m.
  Presenter: Vasileios Paraskevas
  #1302

- Title: Anti-SGSH antibodies following hematopoietic stem cell (HSC) gene therapy in MPSIIIA patients neither impact engraftment of genetically modified HSC nor interfere with multi-compartment substrate reduction
  Date/Time: Thursday, May 15 from 5:30 to 7:00 p.m.
  Presenter: Brian Bigger
  #1513

- Title: Correction of Glycogen Accumulation in Muscle, Heart and CNS in a Pre-Clinical Model of Hematopoietic Stem Cell Gene Therapy for Pompe Disease
  Date/Time: Thursday, May 15 from 5:30 to 7:00 p.m.
  Presenter: Piv Sagoo
  #1514

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 / Libmeldy
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) and UK Medicines and Healthcare products Regulatory Agency (MHRA). 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 DSMO. 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 and deliver novel medicines and treatments 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 with high unmet medical needs, such as bone & mineral, intractable hematological diseases/hemato oncology, and rare diseases. A shared commitment to our values, to sustainable growth, and to making people smile unites us across the globe. You can learn more about the business of Kyowa Kirin at www.kyowakirin.com.

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[i] *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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