Policy Number	**RX501.171**
Policy Effective Date	**12/15/2025**

Gene Therapies for Metachromatic Leukodystrophy

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Related Policies (if applicable)
None

Disclaimer

Medical policies are a set of written guidelines that support current standards of practice. They are based on current generally accepted standards of and developed by nonprofit professional association(s) for the relevant clinical specialty, third-party entities that develop treatment criteria, or other federal or state governmental agencies. A requested therapy must be proven effective for the relevant diagnosis or procedure. For drug therapy, the proposed dose, frequency and duration of therapy must be consistent with recommendations in at least one authoritative source. This medical policy is supported by FDA-approved labeling and/or nationally recognized authoritative references to major drug compendia, peer reviewed scientific literature and generally accepted standards of medical care. These references include, but are not limited to: MCG care guidelines, DrugDex (IIa level of evidence or higher), NCCN Guidelines (IIb level of evidence or higher), NCCN Compendia (IIb level of evidence or higher), professional society guidelines, and CMS coverage policy.

Carefully check state regulations and/or the member contract.

Each benefit plan, summary plan description or contract defines which services are covered, which services are excluded, and which services are subject to dollar caps or other limitations, conditions or exclusions. Members and their providers have the responsibility for consulting the member's benefit plan, summary plan description or contract to determine if there are any exclusions or other benefit limitations applicable to this service or supply. **If there is a discrepancy between a Medical Policy and a member's benefit plan, summary plan description or contract, the benefit plan, summary plan description or contract will govern.**

Legislative Mandates

EXCEPTION: For HCSC members residing in the state of Ohio, § 3923.60 requires any group or individual policy (Small, Mid-Market, Large Groups, Municipalities/Counties/Schools, State Employees, Fully-Insured, PPO, HMO, POS, EPO) that covers prescription drugs to provide for the coverage of any drug approved by the U. S. Food and Drug Administration (FDA) when it is prescribed for a use recognized as safe and effective for the treatment of a given indication in one or more of the standard medical reference compendia adopted by the United States Department of Health and Human Services or in medical literature even if the FDA has not approved the drug for that indication. Medical literature support is only satisfied when safety and efficacy has been confirmed in two articles from major peer-reviewed professional medical journals that present data supporting the proposed off-label use or uses as generally safe and effective. Examples of accepted journals include, but are not limited to, Journal of

American Medical Association (JAMA), New England Journal of Medicine (NEJM), and Lancet. Accepted study designs may include, but are not limited to, randomized, double blind, placebo controlled clinical trials. Evidence limited to case studies or case series is not sufficient to meet the standard of this criterion. Coverage is never required where the FDA has recognized a use to be contraindicated and coverage is not required for non-formulary drugs.

Coverage

Atidarsagene autotemcel

Atidarsagene autotemcel (Lenmeldy™) **may be considered medically necessary** for individuals if they meet criteria 1 through 5:

1. Confirmed diagnosis of metachromatic leukodystrophy (MLD) by gene sequencing and/or deletion/duplication assessment identifies biallelic *human arylsulfatase A (ARSA)* pathogenic or likely pathogenic variants.
2. If a proband individual has all of the following:
    a. ARSA enzyme activity in leukocytes below reference values;
    b. Urinary sulfatide levels above reference values.
3. Confirmed diagnosis of one of the following subtypes of MLD (see Policy Guidelines):
    a. Pre-symptomatic late infantile;
    b. Pre-symptomatic early juvenile;
    c. Early symptomatic early juvenile.
4. Meet the institutional requirements for a stem cell transplant procedure where the individual is expected to receive gene therapy. The requirements may include:
    a. Adequate performance status score (e.g., Karnofsky performance status, Lansky performance status);
    b. Absence of advanced liver disease;
    c. Adequate estimate glomerular filtration rate (eGFR);
    d. Adequate diffusing capacity of the lungs for carbon monoxide (DLCO);
    e. Adequate ventricular ejection fraction (LVEF);
    f. Absence of clinically significant active infection(s).
5. Have not received a previous allogenic hematopoietic stem cell transplant or gene therapy.

Atidarsagene autotemcel **is considered experimental, investigational and/or unproven** when the above criteria are not met.

Atidarsagene autotemcel **is considered experimental, investigational and/or unproven** for all other indications.

Repeat treatment with atidarsagene autotemcel **is considered experimental, investigational and/or unproven**.

Policy Guidelines

Recommended Dose

Metachromatic Leukodystrophy Subtype	Minimum Recommended Dose ($CD34^+$ cells/kg)	Maximum Recommended Dose ($CD34^+$ cells/kg)
Pre-symptomatic late infantile	4.2×10^6	30×10^6
Pre-symptomatic early juvenile	9×10^6	30×10^6
Early symptomatic early juvenile	6.6×10^6	30×10^6

Dosing Limits
1 injection per lifetime

Other Considerations
The U.S. Food and Drug Administration (FDA) approved label includes a normal range for arylsulfatase A (ARSA) enzyme activity to be 31 to 198 nmol/mg/h. Elevated urinary sulfatide levels may differ among laboratory testing facilities.

In the clinical trials of atidarsagene autotemcel, children were classified as having pre-symptomatic late infantile, pre-symptomatic early juvenile, or early symptomatic early juvenile metachromatic leukodystrophy based on the following:

Metachromatic Leukodystrophy Subtype	Disease Classification
Pre-symptomatic late infantile	• Expected disease onset ≤30 months of age • *ARSA* genotype consistent with late infantile • Absence of neurological signs and symptoms
Pre-symptomatic early juvenile	• Expected disease onset >30 months and <7 years of age • *ARSA* genotype consistent with early juvenile • Absence of neurological signs and symptoms or physical exam findings limited to abnormal reflexes and/or clonus
Early symptomatic early juvenile	• Disease onset >30 months and <7 years of age • *ARSA* genotype consistent with early juvenile • Walking independently (GMFC-MLD Level 0 with ataxia or GMFC-MLD Level 1) and IQ ≥ 85

ARSA: *arylsulfatase A* gene; GMFC: Gross Motor Classification; MLD: metachromatic leukodystrophy.

Atidarsagene autotemcel is a lentiviral vector gene therapy which has a potential risk of lentiviral vector-mediated insertional oncogenesis post-treatment. In clinical trials for

atidarsagene autotemcel, no cases of insertional oncogenesis have been reported. Individuals treated with atidarsagene autotemcel may develop hematological malignancies and should be monitored lifelong. Individuals should be monitored with a complete blood count (with differential) annually and integration site analysis as warranted for at least 15 years post-treatment.

Description

Metachromatic Leukodystrophy

Metachromatic leukodystrophy (MLD) is a rare autosomal recessive lysosomal disease that causes progressive demyelination of the central and peripheral nervous system. It is caused by deficient activity of the lysosomal enzyme arylsulfatase A (*ARSA*). The *ARSA* gene, located on chromosome 22q13.3-qter, encodes this enzyme. In almost all cases, biallelic pathogenic variants in the *ARSA* gene lead to MLD. A rare variant form of MLD is caused by a deficiency of sphingolipid activator protein SAP-B (saposin B), which is responsible for the degradation of sulfatides by ARSA. This form is caused by mutations in the *prosaposin* gene (*PSAP* gene). (1)

Numerous pathogenic variants of the ARSA gene have been documented. Among individuals of European descent, 2 specific alleles (A and I) contribute to roughly 50% of cases. (2, 3) However, different populations have different allele distributions. (4) The 2 most common pathogenic variants are described below:

- Homozygosity for the I allele (c.459+1G>A) is the most common of the null alleles (also called "0" alleles), which are pathogenic variants that completely abolish enzyme activity; other common null alleles are c.1210+1G>A and p.Asp257His. These alleles are associated with late infantile onset forms. Compound heterozygotes (with the other allele unknown) also have a late infantile onset. (1)
- Homozygosity for the A allele (p.P426L) is the most common of hypomorphic alleles (also called "R" for residual alleles), which are pathogenic variants that cause reduced but not absent enzyme activity. It is associated with the juvenile- or adult-onset forms; compound heterozygotes have later onset of disease.
- Presence of both I and A alleles is associated with juvenile onset.

The ARSA enzyme is responsible for the breakdown of sulfatides, one of the most common sphingolipids in the myelin sheath. Due to the deficient activity of ARSA enzyme, breakdown of sulfatides is impeded and they accumulate within the central and peripheral nervous system. This accumulation impairs the function and integrity of myelin sheaths, leading to demyelination. Sulfatides can also accumulate in other organs, including the kidneys, testes, and gallbladder. MLD can be classified based on the age of onset and clinical features of the disease. All forms of the disease involve a progressive deterioration of neurodevelopment and neurocognitive function. MLD is categorized based on the age of onset and is summarized in Table 1. Mean survival varies based on subtype, with late infantile MLD children surviving around 8 years and those with early juvenile MLD 10 to 20 years. (5, 6)

Table 1. Clinical Classification of Metachromatic Leukodystrophy

Classification	Onset	Clinical features
Late Infantile form	6 months to 4 years of age	• Most common and most severe form. • Infants and toddlers may present with developmental delay or regression of motor skills due to peripheral neuropathy even before any evidence of brain magnetic resonance imaging changes. In some cases, the first symptoms may be apparent after a febrile illness or anesthesia. (1) Symptoms may then abate for weeks before continuing to progress. Other early signs can include gait difficulties, seizures, ataxia, hypotonia, extensor plantar responses, and optic atrophy. (7, 8) • Deep tendon reflexes are sometimes reduced or absent, reflecting the peripheral neuropathy. Sensory potentials are affected earlier and more severely than are motor responses. (9) • The prognosis is worse than later-onset forms of metachromatic leukodystrophy; progression to death typically occurs within 5 to 6 years, although some patients survive into the second decade of life. (1)
Early Juvenile	4 to 6 years of age	• Heterogeneous in presentation. Some children present between 4 and 6 years of age (early juvenile) while others may present between 6 and 16 years of age (late juvenile). (7, 10) • Children may present with intellectual impairment, behavioral difficulties, gait disturbance, ataxia, upper motor neuron signs, and a peripheral neuropathy; seizures may also occur. • Progression is slower compared with the late infantile form, and these children may survive until early adulthood.
Late Juvenile	6 to 16 years of age	
Adult form	Beyond 16 years of age	• Least common form, is usually heralded by dementia and behavioral difficulties, and a substantial minority present with neuropathy, psychosis, schizophrenia, or seizures. (7, 11) Optic atrophy has also been reported. (12) • A late-onset or adult-onset phenotype limited to psychiatric disease with minimal or no motor findings is well described but often remains undiagnosed for many years; the course is static or very slowly progressive. (13) Affected patients may survive for 20 to 30 years after onset. (11)

Epidemiology

The prevalence of MLD ranges from 1 in 40,000 to 1 in 100,000 in the northern European and North American populations. (14) However, a higher prevalence has been found in certain groups, including Habbanite Jews in Israel, Arabs living in Israel, and Navajo Indians in the United States. (15-17) Incidence is estimated to be 1/40,000 births in the United States. There is no sexual and racial predilection.

Diagnosis

Leukodystrophies are generally suspected in pediatric patients with difficulties in meeting appropriate development milestones when previously able to do so. Peripheral neuropathy can present prior to dysarthria and other CNS manifestations. (18) A decline in gross and fine motor skills at any age should be evaluated for MLD. Diagnosis can be challenging for the late infantile form, as the brain MRI may be normal initially and the early presenting symptoms of hyporeflexia and developmental delay are relatively nonspecific. In a patient with progressive neurologic dysfunction and/or leukodystrophy, the diagnosis of MLD due to ARSA deficiency is established when all of the following criteria are met:

- Genetic test identifies biallelic *ARSA* pathogenic variants.
- Enzyme assay confirms deficient ARSA enzyme activity in leukocytes. In individuals with MLD, ARSA activity levels typically range from undetectable to less than 10 percent of normal values.
- Sulfatide measurement reveals elevated levels in urine.

Elevated urinary sulfatides are present in all types of MLD, including MLD due to sphingolipid activator protein B (Sap-B) deficiency. (1, 19, 20) Both enzyme assay and sulfatide substrate measurement are essential parts of the biochemical diagnosis. They complement gene sequencing, especially in the case of a proband. For siblings of an index case, gene sequencing alone is sufficient. Additionally, assessing both enzyme activity and sulfatides aids in distinguishing ARSA pseudodeficiency from MLD. ARSA pseudodeficiency refers to individuals who have non-disease-causing pseudodeficiency alleles in the *ARSA* gene which results in low ARSA enzyme activity levels approximating those of patients with MLD. Thus, the diagnosis of MLD should not be based only on the activity of ARSA; screening for pseudodeficiency alleles is important when low, but not absent, levels of ARSA are detected. (21) ARSA pseudodeficiency is present in approximately 1 percent of the general population.

Delays in diagnosis and misdiagnosis are common in children without a diagnosed sibling, with the time from first symptom to diagnosis of 4 months to 1 year with late infantile MLD and up to seven years for children with juvenile MLD. (22)

Availability of newborn screening for MLD is limited and is not yet recommended in the United States by the federal Recommended Uniform Screening Panel. (23) Newborn screening for MLD, based on detection of elevated blood sulfatide levels, is occurring in Germany and in New York. (24)

Treatment

Allogeneic hematopoietic stem cell transplant (HSCT) has been used for years but has yielded mixed results. (25) Engraftment typically requires myeloablative conditioning, often with high doses of busulfan, which can cross the blood-brain barrier and cause neurologic decline. Despite significant advancements in allogeneic transplantation, this therapeutic approach continues to be a topic of controversy for several reasons. Firstly, systematic outcome data are scarce and challenging to generalize due to variations in eligibility criteria and transplantation protocols across different studies. Secondly, relying on outcome data from older patient cohorts may not accurately predict current results given constantly improving transplant-related morbidity and mortality due to advances in donor-recipient human leukocyte antigen typing and matching, conditioning, infectious disease detection and management, and the use of non-carrier donors. Lastly, different types of MLDs have shown varying responses.

Allogeneic HSCT has been found to be ineffective for late infantile or early juvenile forms and is not recommended for this population. (25) Allogeneic HSCT may provide some benefit in late-onset MLD who are pre-symptomatic or minimally symptomatic at the time of transplant. (26-31) In a 2023 systematic review, disease progression at 10 years involving decreased motor function or loss of language occurred in 8 of 20 patients (40 percent) with juvenile onset who received HSCT compared with 28 of 41 patients (68%) with juvenile onset who did not receive HSCT. (32) In a single-center cohort report with 16 evaluable long-term (10-year) MLD survivors who received HSCT, the investigators concluded that the aggregate motor and language function was favorable compared with the natural history. (27)

Regulatory Status

On March 18, 2024, Lenmeldy™ (atidarsagene autotemcel) was approved by the Food and Drug Administration (FDA) for the treatment of children with pre-symptomatic late infantile, pre-symptomatic early juvenile, or early symptomatic early juvenile metachromatic leukodystrophy.

Rationale

Medical policies assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are length of life, quality of life, and ability to function including benefits and harms. Every clinical condition has specific outcomes that are important to patients and to managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of a technology, 2 domains are examined: the relevance and the quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The

quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. Randomized controlled trials (RCTs) are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

Metachromatic Leukodystrophy

Clinical Context and Therapy Purpose

The purpose of gene therapies in individuals with metachromatic leukodystrophy (MLD) is to provide a treatment option that is an improvement on existing therapies. Potential benefits of this one-time therapy may include the following:

- Novel mechanism of action or approach may allow successful treatment of patients for whom other available treatments have failed.
- Successful treatment may reduce the potential for disease and standard treatment-related morbidity and mortality and improve quality of life.

The following PICO was used to select literature to inform this policy.

Populations

The relevant populations of interest are children with pre-symptomatic late infantile, pre-symptomatic early juvenile, or early symptomatic early juvenile MLD.

Interventions

The therapy being considered is atidarsagene autotemcel. In this gene therapy protocol, hematopoietic stem cells are mobilized using granulocyte colony-stimulating factor (G-CSF) with or without plerixafor followed by apheresis to obtain a CD34+ cell-enriched population. These cells are then transduced *ex vivo* by lentiviral vector encoding the *human arylsulfatase A (ARSA)* gene. Individuals receive myeloablative conditioning with busulfan to deplete endogenous hematopoietic stem cells and lymphodepletion with cyclophosphamide, enabling therapeutic repopulation of the individual bone marrow with hematopoietic stem cells containing the transgene. Treatment with atidarsagene autotemcel requires inpatient hospitalization. Atidarsagene autotemcel aims to correct the underlying genetic cause of MLD. When the genetically repaired cells are infused back into the individual, 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.

Comparators

The following strategies are currently being used to make decisions about allogenic hematopoietic stem cell transplantation and multidisciplinary supportive care to improve quality of life, maximize function, and reduce complications.

Outcomes

The general outcomes of interest are overall survival, disease-specific survival, change in disease status, functional outcomes, quality of life, treatment-related morbidity, and treatment-related mortality (Table 2). Follow-up at 15 years is of interest to monitor outcomes.

Table 2. Health Outcome Measures Relevant to Metachromatic Leukodystrophy

Outcome	Measure (Units)	Description and Administration	Thresholds for Improvement/Decline or Clinically Meaningful Difference (if known)
Cognitive function	Neuropsychological tests (Bayley Scale of Infant Development, Wechsler Preschool and Primary Scale of Intelligence, Wechsler Intelligence Scale for Children, or Wechsler Adult Intelligence Scale) according to the child's age and/or ability.	According to the child's age and/or ability.	When assessed within the appropriate age ranges, a standard score can be derived, allowing comparison of a child's cognitive ability with the normative population. In trials, cognitive function was defined using the following: • Normal cognitive function, standard score ≥85; • Mild cognitive impairment, standard score ≥70 and <85; • Moderate cognitive impairment, score >55 and <70; • Severe cognitive impairment, score ≤55.
Motor function	Gross motor function classification (GMFC-MLD).	Levels of GMFC-MLD (33) • 0=Walking without support with quality of performance normal for age. • 1= Walking without support but with reduced quality of performance (i.e., instability when standing or walking).	

		• 2= Walking with support. Walking without support not possible (fewer than 5 steps). • 3= Sitting without support and locomotion such as crawling or rolling. Walking with or without support not possible. • 4= Sitting without support but no locomotion or sitting without support not possible, but locomotion such as crawling or rolling possible. • 5= No locomotion nor sitting without support, but head control is possible. • 6= Loss of any locomotion as well as loss of any head and trunk control.	

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.

- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Consistent with a 'best available evidence approach,' within each category of study design, studies with larger sample sizes and longer durations were sought.
- Studies with duplicative or overlapping populations were excluded.

The clinical development program is summarized in Table 3. The U.S. Food and Drug Administration (FDA) approval was based on the integrated efficacy analyses of the comparisons between 2 groups of pooled data. The pooled treated group included data from 39 individuals (n=18 from study 201222, n=10 from study 205756 and n=9 from a European Union expanded access program). The protocols for these studies did not differ substantially in their study design, eligibility criteria, and assessment schedule, thus supporting a pooled analysis. Differences across protocols stemmed from differences in myeloablative conditioning regimens, source of the CD34+ cells for transduction (bone marrow versus mobilized peripheral blood) and formulation of the drug product (fresh versus cryopreserved); these differences did not lead to differences in clinical outcomes. Two children with advanced disease were excluded from the efficacy analysis yielding a final sample of 37. The untreated natural history group consisted of 49 individuals (n=43 from study 204949 and 6 untreated siblings of individuals enrolled in study 205756). Natural history data was collected retrospectively through chart review and parental interviews and through prospective in-person assessments of the child. (34-36)

Pivotal Study

Study characteristics, baseline patient characteristics, and results are summarized in Tables 3 to 6, respectively. In the trials, subgroups of MLD were classified as follows:

- Pre-symptomatic late infantile MLD: Children with expected disease onset ≤30 months of age and an ARSA genotype consistent with late infantile MLD. Pre-symptomatic status was defined as the absence of neurological signs and symptoms of MLD.
- Pre-symptomatic early juvenile MLD: Children with expected disease onset >30 months and <7 years of age and an ARSA genotype consistent with early juvenile MLD. Pre-symptomatic was defined as the absence of neurological signs and symptoms of MLD or physical exam findings limited to abnormal reflexes and/or clonus.
- Early symptomatic early juvenile MLD: Children with disease onset >30 months and <7 years of age and an ARSA genotype consistent with early juvenile MLD. Early symptomatic status was defined as walking independently (Gross Motor Classification [GMFC]-MLD level 0 with ataxia or GMFC-MLD level 1) and IQ ≥ 85. Note that the original protocol defined early symptomatic early juvenile MLD as IQ ≥70 and the ability to take ≥10 steps independently. However, a post-hoc analysis of treatment failures done during the evaluation process by the European Medicines Agency suggested that treatment was not effective below certain thresholds of cognitive and motor function. Thus, the protocol was amended to include only MLD patients with IQ ≥85 and GMFC-MLD level ≤1.

Pre-symptomatic Late Infantile
In this subgroup, there were 20 treated patients and 28 untreated patients from natural history cohort. None of the 17 children treated with atidarsagene autotemcel who were followed until 5 years of age progressed to severe motor impairment, while 100% of the 28 children in the natural history cohort did. Efficacy of atidarsagene autotemcel was also seen on survival, where 100% of the 14 treated children who were followed until 6 years of age were alive, compared to only 58% of the 24 untreated children in the natural history cohort. Detailed results are summarized in Table 6.

Pre-symptomatic Early Juvenile
In this subgroup, there were 7 treated patients and 21 untreated patients from natural history cohort. Children were between 11 and 67 months (median 31 months) of age at the time of treatment with atidarsagene autotemcel. Of the 7 treated children, 1 (14%) child died at age 2.1 years from a cerebral infarction. Of the remaining 6, there were insufficient data in 3 children who were too young at last follow-up to evaluate efficacy of atidarsagene autotemcel as symptom onset may not begin until 7 years of age. Because of the small sample size and large heterogeneity in this population as well as questionable comparability with the natural history cohort, the FDA statistical reviewer concluded that the pre-specified comparative analyses of the efficacy endpoints would not provide meaningful information. Therefore, the efficacy was evaluated descriptively, rather than being evaluated via confirmatory statistical hypothesis testing. (34)

Data from 3 children is summarized in Table 6. Two had evaluable motor and cognitive outcomes while one had evaluable motor outcomes, but while showing stable normal cognitive function, was neither old enough nor had sibling data for cognitive events to be evaluable. Three children retained independent ambulation (GMFC-MLD ≤ Level 1) at last follow-up at ages 8.3, 11.0 and 13.6 years. Additionally, all 3 children retained cognitive functioning in the "broadly average" range (performance and language standard scores ≥85). Based on the published natural history of early juvenile MLD, untreated early juvenile MLD patients would be expected to lose independent ambulation (GMFC-MLD ≥ Level 2) and experience impairment in cognitive functioning at those ages. (5, 33) Three other children were still under 7 years of age at time of last follow-up, and as early juvenile MLD may be asymptomatic until 7 years of age, it is premature to detect clinical outcomes that deviate from the natural history in these children. It is unknown whether atidarsagene autotemcel impacts survival in pre-symptomatic MLD as the duration of follow-up was limited; untreated children with early juvenile MLD may not progress to death until adulthood.

Early-symptomatic Early Juvenile
In this subgroup, there were 10 treated patients. Two children (20%) died from MLD disease progression 8 and 15 months after treatment with atidarsagene autotemcel. In the final analysis, data from 7 treated children were included. The same 21 untreated early juvenile subjects from natural history cohort used in the analyses for pre-symptomatic early juvenile subgroup was used in the analyses for early-symptomatic early juvenile subgroup. Children developed symptom onset prior to treatment between 29 and 83 months of age (median 62

months) and were treated with atidarsagene autotemcel between 31 and 140 months (median 70 months). All treated children experienced motor disease progression after treatment that did not appear slowed when compared to the natural history children. However, clinical benefit of atidarsagene autotemcel was observed in the slowing of cognitive disease progression in the treated children. Four children (40%) retained normal performance standard scores (≥85) and 3 of these children retained normal language standard scores (≥85) between the ages of 13 and 16 years. Preservation of cognitive functioning in these 4 children occurred despite progression of motor disease. This is unexpected in the natural history of early juvenile MLD where cognitive and motor functioning are expected to decline in parallel, with significant cognitive impairment expected by adolescence. (33)

Safety

Safety data includes data from 39 study participants treated in clinical trials. (34, 35) The median (range) years of follow-up was 6.8 years (0.6-12.2). Three deaths were reported in the clinical development program. Two deaths in study 201222 were attributed to rapid progression of underlying disease that eventually led to severe dysphagia. The study participants died at 8- and 15-months post-gene therapy. One death in the expanded access program occurred at approximately 14 months post-gene therapy due to left hemisphere cerebral ischemic stroke. These events were not considered to be related to gene therapy by the investigators. The only treatment-related adverse event in the atidarsagene autotemcel clinical development program was anti-ARSA antibodies in 6 participants. No evidence of malignancy, clonal expansion, or insertional oncogenesis associated with atidarsagene autotemcel were observed. Additional risks of atidarsagene autotemcel observed in the clinical trial include serious infections (occurred in 39% of all children, including 2 events of sepsis), veno-occlusive disease (occurred in 8% of children, with no events meeting Hy's law criteria), and delayed platelet engraftment (platelet engraftment after day 60 occurred in 10% of all children). Other adverse reactions were related to myeloablative conditioning or underlying disease. Finally, six patients developed anti-ARSA antibodies. Although these antibodies resolved in all patients, some patients were treated with rituximab therapy. It is also not clear what the potential long-term impact of anti-ARSA antibodies may be, and whether they may impact long-term response. (37)

Table 3. Summary of the Clinical Development Program for Atidarsagene Autotemcel

Study	Study 201222	Study 205756	EAP	Study 204949 NHx
NCT Number	NCT01560182	NCT03392987	Not available	Not available
Phase	1/2	1/2	-	Natural history
Study Population	Individuals with early-onset MLD (late infantile to early juvenile)	Individuals with early-onset MLD (late infantile to early juvenile)	Individuals with early-onset MLD (late infantile to early juvenile)	Individuals with early-onset MLD who did not receive any treatments for MLD apart from supportive care

Status	Started on April 9, 2010, at Ospedale San Raffaele, in Milan, Italy. Completed and published. (38, 39)	Started on January 25, 2018, at the Ospedale San Raffaele Telethon Institute for Gene Therapy, in Milan, Italy. As of November 2022.	Dates for enrollment not available. Study conducted at the Ospedale San Raffaele Telethon Institute for Gene Therapy, in Milan, Italy.	Dates for enrollment not available. Study conducted at the Ospedale San Raffaele Telethon Institute for Gene Therapy, in Milan, Italy.
Study Dates	2010-2018	2018-ongoing	Not available	Not available
Design	Single arm, single center	Single arm, single center	Single arm, single center	Observational, single arm, single center
Sample Size	20[a]	10	9	43
Follow-Up	24 months	24 months	Unknown	Unknown

MLD: metachromatic leukodystrophy; NCT national clinical trial.

[a] The study included 20 patients, but analysis was conducted on 29 patients: 20 from the study and 9 from an expanded access program.

Table 4. Summary of Key Nonrandomized Trial

Study	NCT01560182	NCT03392987	Integrated analysis
Study Type	Single-arm, prospective	Single-arm, prospective	Pooled data from NCT01560182 (n=18), NCT0339298737 (n=10), and a European Union Expanded Access Program (n=9)
Country	Italy	Italy	Italy
Dates	2010-2018	2018-ongoing	Information not available
Participants	**Inclusion criterion** • Age ≤7 years • Pre-symptomatic[a] with late infantile variant[b] or pre-symptomatic or early symptomatic[c] with early juvenile variant[d] **Exclusion criterion**	**Inclusion criterion** • Children ≤6 years of age • Diagnosis of MLD confirmed by evaluation of ARSA activity and identification of 2 ARSA alleles with	**Primary endpoint** • Severe motor impairment-free survival defined as the time interval from birth to the first occurrence of loss of locomotion and

	• HIV virus, hepatitis C and/or hepatitis B virus positive • Neoplastic disease • Cytogenetic alteration typical of myelodysplastic syndrome or acute myeloid leukemia • End-organ dysfunction or other severe disease • Allogenic hematopoietic stem cell transplant in past 6 months or evidence of residual cells of donor origin **Co-primary endpoints:** • >10% improvement in total GMFC score in treated patients compared with natural history cohort patients at year 2 post treatment • Increase in residual ARSA activity in peripheral blood mononuclear cells from baseline to year 2 post treatment compared with pretreatment values **Secondary endpoints:** • Safety	mutations that cause disease. • Early-onset MLD, demonstrated by either an older sibling with MLD whose onset of symptoms was at ≤6 years of age or approval by the Orchard medical monitor if the child has an early-onset variant of MLD that was detected pre-symptomatically in a patient without an older sibling with MLD.[f] **Primary endpoint** • Change in gross motor function measure score at 24 months post gene therapy	loss of sitting without support (GMFC-MLD level ≥5) or death. **Secondary endpoints** • Proportion of individuals who had experienced severe motor impairment or death by year 2 post-treatment evaluated in a subset of matched subjects. Similar analyses for year 5 post-treatment were also performed in a descriptive manner. • Overall survival defined as the time interval between birth and death from any cause. **Additional outcomes** • Descriptive results on motor function progression to lower severity levels of GMFC-MLD and cognitive function, in terms of performance and language standard scores, were considered as other important

			measures for efficacy.
Treatment	Atidarsagene autotemcel by IV infusion (fresh formulation): 2-20 x 10^6 CD34+ cells/kg (n=20)	Atidarsagene autotemcel by IV infusion (cryopreserved formulation): (3-30 × 10^6 CD34+ cells/kg) (n=10)	-
Follow-Up	Primary follow-up completed 24 months post gene therapy, with additional follow-up visits to be conducted over a period of 8 years post gene therapy	Primary follow-up completed 24 months post gene therapy, with additional follow-up visits to be conducted over a period of 8 years post gene therapy	Median follow-up 6.8 years (0.6, 12.2) for safety analysis

ARSA: arylsulfatase A; GMFC: Gross Motor Classification; HIV: human immunodeficiency virus; IV: intravenous; MLD: metachromatic leukodystrophy; NCT: national clinical trial.

[a] Pre-symptomatic: No disease-related neurological impairment with or without signs of disease revealed by instrumentational evaluation

[b] Late infantile: 2 of 3 criteria met (age at onset of symptoms in older sibling ≤30 months, 2 null [0] mutant arylsulfatase A [ARSA] allele[s], peripheral neuropathy at electroneurographic study)

[c] Early symptomatic: 2 criteria met (intelligence quotient [IQ] ≥70 and ability to walk independently for ≥10 steps)

[d] Early juvenile: 2 of 3 criteria met (age at onset of symptoms in subject or older sibling between 30 months and 6 years, 1 null [0] and 1 residual [R] mutant ARSA allele[s], peripheral neuropathy at electroneurographic study)

[e] As of the 2018 data cut

[f] Classification of disease was based on age of diagnosis and genotype; LI: Symptom onset at ≤30 months of age and genotype typically 0/0; EJ: symptom onset >30 months and ≤6 years of age and genotype typically 0/R. Patients may be classified as intermediate LI/EJ if the case cannot be characterized unambiguously.

Table 5. Summary of Baseline Demographics and Disease Characteristics in the Pivotal Integrated Analysis (36)

Characteristic	**Pre-symptomatic late infantile (N=20)**	**Pre-symptomatic early juvenile (N=7)**	**Pre-symptomatic early juvenile (N=10)**
Median age at treatment, months (range)	12 (8, 19)	31 (11, 67)	70 (31, 140)
Male, n (%)	13 (65)	6 (86)	6 (60)
Race, n (%)			
White/Caucasian	18 (90)	6 (86)	10 (100)
Asian	2 (10)	0	0
Black or African American	0	1 (14)	0

Ethnicity – Hispanic or Latino, n (%)	1 (5)	0	0

N/n: number.

Table 6. Summary of Results in the Pivotal Integrated Analysis

Outcomes	Treated	Natural History
Pre-symptomatic late infantile (34, 36)	N=20	N=28
Severe motor impairment or death, n/N (%)	1/20 (5)	28/28 (100)
Kaplan Meir estimate for event-free survival up to 5 years of age	100%	0%
Survival at 6 years of age, n/N (%)	14/14 (100%)	14/24 (58%)
Severe motor impairment or death by 2 years post-treatment, n/N (%)	0/20 (0)	15/25 (60%)
Severe motor impairment or death by 5 years post-treatment, n/N (%)	2/13 (15%)	26/26 (100%)
Cognitive function[a]	19/20 >55 through to the last follow-up. At the last assessment, 2 of these individuals were below the threshold for moderate impairment (< 70), with all others maintaining ≥ 70 and most maintaining normal scores (≥ 85).	All had severe cognitive performance and language impairment (≤55).
Pre-symptomatic early juvenile (34, 36)	N=7	N=21
Motor function	3 of 7 children had evaluable motor outcomes:[b] • Child 1 treated at 4.1 years of age retained normal gait (GMFC-MLD Level 0) at age 11.9 years.	• Matched sibling comparator of child 1 lost all motor function (GMFC-MLD Level 6) by age 6 years. • Matched sibling comparator of child 2 developed impaired gait

	• Child 2 treated at 3.6 years of age retained normal gait (GMFC-MLD Level 0) at age 7.3 years. • Child 3 treated at 5.6 years of age retained normal gait (GMFC-MLD Level 0) until age 12.8 years and still had independent ambulation (GMFC-MLD Level 1) at 13.6 years of age.	(GMFC-MLD Level 1) at age 5 years. • Comparator data not available for child 3.
Cognitive function	2 of 7 children had evaluable cognitive outcomes:[b] • One child treated at 4.1 years of age retained stable normal cognitive function (performance and language standard scores[c] of 130 and 122, respectively) at age 11.9 years. • One child treated at 5.6 years of age retained stable normal performance standard score[c] (116 at 11.4 years). While language standard score remained normal (86 at 11.4 years), it declined from 102 at baseline.	Not available
Early-symptomatic early juvenile (34, 36)	N=10	N=21[d]
Severe motor impairment or death at year 2, n/N (%)	2/10 (20%)	2/15 (13%)
Severe motor impairment or death at year 5, n/N (%)	2/8 (25%)	11/12 (92%)
Died, n/N (%)	2/10 (20%)	3/21 (14%)

	Normal performance standard scores (≥85) between the ages of 13 and 16 years, n/N (%)	4/10 (40%)	Motor functioning is expected to decline by adolescence.
	Normal language standard scores (≥85) between the ages of 13 and 16 years, n/N (%)	3/10 (30%)	Cognitive functioning is expected to decline by adolescence.

GMFC: Gross Motor Classification; MLD: metachromatic leukodystrophy; n/N: number.

[a] Cognitive function was defined using the following: normal cognitive function, standard score ≥ 85; mild cognitive impairment, standard score ≥ 70 and < 85; moderate cognitive impairment, score >55 and < 70; severe cognitive impairment, score ≤ 55

[b] As per the FDA statistical review, because of the small sample size and large heterogeneity in this population as well as questionable comparability with the natural history early juvenile MELD patients, the pre-specified comparative analyses of the efficacy endpoints would not provide meaningful information. Therefore, the efficacy was evaluated descriptively based on clinical knowledge and expectation of similar subjects in the literature, rather than being evaluated via confirmatory statistical hypothesis testing.

[c] Standard scores were derived, allowing comparison of a child's cognitive ability with the normative population.

[d] The same 21 untreated early juvenile patients from natural history cohort used in the analyses for pre-symptomatic early juvenile was used in the analyses for early-symptomatic early juvenile patients.

The purpose of the study limitations tables is to display notable limitations identified in each study. This information is synthesized as a summary of the body of evidence following each table and provides the conclusions on the sufficiency of evidence supporting the position statement. Multiple limitations were noted.

- The FDA approved atidarsagene autotemcel based on a pooled analysis of multiple single-arm studies. Results from single arm studies are susceptible to biases as there may be differences between the treated population and the control arm that are not accounted for, affecting the estimates of treatment differences. Additionally, data in the natural history cohort was sparser than in the trial patients – for example, only baseline ARSA levels were known and other outcomes such as GMFC scores and measures of cognitive function were not necessarily collected at the same timepoints in the natural history cohort as in the trial making direct comparisons difficult. However, given MLD's rarity, using single-arm studies and an external natural history cohort as comparators is reasonable.
- Treatment with atidarsagene autotemcel resulted in robust and large treatment effects among individuals with pre-symptomatic late-infantile MLD which guards it against potential biases noted above. However, the statistical evidence for treatment effects in the pre-symptomatic and early symptomatic early juvenile MLD patients was limited. This was due to small sample sizes and high heterogeneity of the disease trajectories in these populations as well as questionable comparability with the natural history cohort. Nevertheless, individual data evaluations suggested that atidarsagene autotemcel was

clinically beneficial for individuals in terms of motor functions. Furthermore, although cognitive function endpoints were analyzed in a descriptive manner, the observed treatment effects on cognitive function appeared to be substantial for most individuals.

- There were also instances of missing data or inappropriate exclusions. Two patients with early symptomatic early juvenile died due to disease progression after treatment. These 2 patients were ultimately not included in the primary survival analysis due to not meeting the more stringent treatment entry criteria established after they were recruited into the study and based on post-hoc analysis of the data. Removal of these 2 patients creates greater uncertainty about the potential harms in the early symptomatic early juvenile MLD population.
- The long-term durability of atidarsagene autotemcel remains uncertain. Patients are typically treated in infancy or early childhood, and follow-up in current studies spans from 2.4 to 11 years for late infantile patients and 0.6 to 9.2 years for early juvenile MLD patients. While ARSA levels have not significantly declined over time in most patients, the optimal ARSA level required to prevent disease progression remains uncertain due to the lack of correlation between ARSA levels and clinical outcomes. ARSA activity levels increased in all groups to normal or supranormal levels after treatment. Data on 35 MLD patients with up to 11 years of follow-up show that none of the treated patients had PBMC ARSA activity level below the reference range during extended follow-up. Additionally, a few patients did have progression of disease, and it is not clear whether those patients were treated too late in the disease course to prevent disability or whether there are other factors besides ARSA levels that affect disease progression, since all patients were fully engrafted after atidarsagene autotemcel treatment.
- The limited sample sizes of the studies also create uncertainty around the estimates of some of the patient-important outcomes, particularly adverse events. Some serious harms are likely rare occurrences and as such may not be observed in trials. While most of the serious adverse events were attributable to known risks associated with myeloablative conditioning, uncertainty still remains about risk of hematologic malignancy. While no cases of malignancy, clonal expansion, or insertional oncogenesis were reported in the trial participants, such risk cannot be ruled in the larger, real-world, population. There is a risk of oncogenesis with lentiviral vectors and given that patients will be treated early on in life, this will be an important long-term harm to evaluate. Long-term follow-up (>15 years) is required to establish precision around side effects.

Table 7. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-up[e]
Integrated analysis (34, 36)		1. Not clearly defined 5. Other (non-contemporaneous historical control, baseline			1. Not sufficient duration for benefit 2. Not sufficient

		characteristics not reported)			duration for harms

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

[a] Population key: 1. Intended use population unclear; 2. Study population is unclear; 3. Study population not representative of intended use; 4, Enrolled populations do not reflect relevant diversity; 5. Other.

[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest (e.g., proposed as an adjunct but not tested as such); 5: Other.

[c] Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively; 5. Other.

[d] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. Incomplete reporting of harms; 4. Not establish and validated measurements; 5. Clinically significant difference not prespecified; 6. Clinically significant difference not supported; 7. Other.

[e] Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms; 3. Other.

Table 8. Study Design and Conduct Limitations

Study	Integrated analysis (34, 36)
Allocation[a]	1. Participants not randomly allocated 2. Allocation not concealed 3. Allocation concealment unclear 4. Inadequate control for selection bias
Blinding[b]	1. Participants or study staff not blinded 2. Outcome assessors not blinded 3. Outcome assessed by treating physician 4. Outcomes not assessed centrally
Selective Reporting[c]	4. Other (post-hoc sub-group analysis not pre-specified)
Data Completeness[d]	1. High loss to follow-up or missing data 2. Inadequate handling of missing data 5. Inappropriate exclusions
Power[e]	1. Power calculations not reported 2. Power not calculated for primary outcome 3. Power not based on clinically important difference
Statistical[f]	

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

[a] Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias; 5. Other.

[b] Blinding key: 1. Participants or study staff not blinded; 2. Outcome assessors not blinded; 3. Outcome assessed by treating physician; 4. Other.

[c] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication; 4. Other.

[d] Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6.

Not intent to treat analysis (per protocol for noninferiority trials); 7. Other.
[e] Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference; 4. Other.
[f] Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated; 5. Other.

Section Summary: Metachromatic Leukodystrophy

Evidence includes integrated efficacy analyses of several single arm studies compared with an external natural history cohort. The interventional studies enrolled 39 patients with late infantile and early juvenile MLD. In children with pre-symptomatic late infantile MLD (n=21), treatment with atidarsagene autotemcel demonstrated improvement in severe motor impairment-free survival defined as the interval from birth to the first occurrence of loss of locomotion and loss of sitting without support or death, and in survival and cognitive function outcomes when compared to natural history cohort (n=28). In children with pre-symptomatic early juvenile MLD (n=7), the effectiveness of atidarsagene autotemcel was demonstrated by slowing of the progression of motor and cognitive disease manifestations compared to untreated children and matched sibling comparators. In children with early-symptomatic early juvenile MLD (n=10), atidarsagene autotemcel effectiveness was demonstrated in a subject-level analysis which showed slowing of cognitive disease progression despite continued progression of motor disease in treated children, which is unexpected in untreated patients. The major risks of atidarsagene autotemcel treatment include thrombosis and thromboembolic events, encephalitis, serious infection, veno-occlusive disease, and delayed platelet engraftment. In the context of MLD, the associated risks are deemed acceptable due to the severity of the disease and the lack of effective standard treatments. Notable limitations include use of single arm studies with an external historical cohort which are susceptible to biases that may affect the estimates of treatment differences. Additionally, the sample sizes were limited with high heterogeneity of the disease trajectories in patients with pre-symptomatic or early symptomatic early juvenile MLD. There were also instances of missing data or inappropriate exclusions. In addition, there are uncertainties about long-term durability and safety. While no cases of malignancy, clonal expansion, or insertional oncogenesis were reported in the trial participants, such risk cannot be ruled out in the larger, real-world, population. There is a risk of oncogenesis with lentiviral vectors and, given that patients will be treated early on in life, this will be an important long-term harm to evaluate.

Summary of Evidence

For individuals with pre-symptomatic late infantile, pre-symptomatic early juvenile, or early symptomatic early juvenile metachromatic leukodystrophy (MLD) who receive atidarsagene autotemcel, the evidence includes integrated efficacy analyses of several single arm studies compared with an external natural history cohort. The interventional studies enrolled 39 patients with late infantile and early juvenile MLD. All study participants were classified as having MLD on the basis of 2 known pathologic mutations in the *ARSA* gene, 2 null mutations for pre-symptomatic late infantile and at least 1 mutation encoding residual enzyme for pre-symptomatic or early symptomatic early juvenile MLD. Late infantile was defined as expected

disease onset ≤30 months of age while early juvenile was defined as expected or actual disease onset >30 months and <7 years of age. Pre-symptomatic status was defined as the absence of neurological signs and symptoms of MLD, or physical exam findings limited to abnormal reflexes and/or clonus. Early symptomatic status was defined as walking independently and IQ ≥85. In children with pre-symptomatic late infantile MLD (n=21), treatment with atidarsagene autotemcel demonstrated improvement in severe motor impairment-free survival (defined as the interval from birth to the first occurrence of loss of locomotion and loss of sitting without support or death), and in survival and cognitive function outcomes when compared to natural history cohort (n=28). In children with pre-symptomatic early juvenile MLD (n=7), the effectiveness of atidarsagene autotemcel was demonstrated by slowing of the progression of motor and cognitive disease manifestations compared to untreated children and matched sibling comparators. In children with early symptomatic early juvenile MLD (n=10), atidarsagene autotemcel effectiveness was demonstrated in a subject-level analysis which showed slowing of cognitive disease progression despite continued progression of motor disease in treated children, which is unexpected in untreated patients. The major risks of atidarsagene autotemcel treatment include thrombosis and thromboembolic events, encephalitis, serious infection, veno-occlusive disease, and delayed platelet engraftment. In the context of MLD, the associated risks are deemed acceptable due to the severity of the disease and the lack of effective standard treatments. Notable limitations include use of single arm studies with an external historical cohort which are susceptible to biases that may affect the estimates of treatment differences. Additionally, the sample size was limited with high heterogeneity of the disease trajectories in patients with pre-symptomatic or early symptomatic early juvenile MLD. There were also instances of missing data or inappropriate exclusions. Two patients with early symptomatic early juvenile died due to disease progression after treatment. These 2 patients were ultimately not included in the primary survival analysis due to not meeting the more stringent treatment entry criteria established after they were recruited into the study and based on post-hoc analysis of the data. Removal of these 2 patients creates greater uncertainty about the potential harms in the early symptomatic early juvenile MLD population. In addition, there are uncertainties about long-term durability and safety. While no cases of malignancy, clonal expansion, or insertional oncogenesis were reported in the trial participants, such risk cannot be ruled out in the larger, real-world, population. There is a risk of oncogenesis with lentiviral vectors and, given that patients will be treated early on in life, this will be an important long-term harm to evaluate. While there is residual uncertainty around the estimates of some of the clinical outcomes, the observed magnitude of the benefit indicates that atidarsagene autotemcel will frequently be successful in treating patients with late infantile or early juvenile MLD especially when given in pre-symptomatic phase. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

Practice Guidelines and Position Statements

American College of Medical Genetics and Genomics (ACMG)

The ACMG work group published a consensus-based guidelines in 2011 for the diagnostic confirmation and management of individuals identified by newborn screening, family-based testing after proband identification, or carrier testing in at-risk populations, and subsequent

prenatal or postnatal testing of those who are pre-symptomatic for a lysosomal storage disease. (25)

In the section for MLD (OMIM# 250100), the following observations were made regarding management of individuals with MLD:

- For late infantile MLD, no approved specific therapy exists at all, and treatment efforts are restricted to palliative and/or supportive measures including the prevention or delay of secondary complications.
- Early HSCT at a pre-symptomatic stage is completely ineffective and is not recommended.
- Because of the less rapid disease progression, HSCT has been established for several years as the only specific therapeutic option for juvenile and adult forms of MLD.

Institute for Clinical and Economic Review

The Institute for Clinical and Economic Review published a final report on atidarsagene autotemcel for MLD on October 30, 2023. (37) The Report concluded that

- For children with pre-symptomatic late infantile and pre-symptomatic early juvenile MLD, there is high certainty that treatment with atidarsagene autotemcel has substantial net health benefit ("A") versus standard of care.
- For children with early-symptomatic early juvenile MLD, there is moderate certainty of a small or substantial net health benefit with high certainty of at least a small net health benefit ("B+") versus standard of care.

National Institute for Health and Care Excellence

The National Institute for Health and Care Excellence published a highly specialized technologies guidance report on atidarsagene autotemcel for treating MLD on March 28, 2022. (40) The guidance report makes the following recommendations:

Atidarsagene autotemcel is recommended, within its marketing authorization, as an option for treating metachromatic leukodystrophy with mutations in the *ARSA* gene:

- For children who have late infantile or early juvenile types, with no clinical signs or symptoms.
- For children who have the early juvenile type, with early clinical signs or symptoms, and who can still walk independently and have no cognitive decline.

It is recommended only if the company provides atidarsagene autotemcel according to the commercial arrangement.

Atidarsagene autotemcel should be delivered in a highly specialized service by a specialist multidisciplinary team.

Ongoing and Unpublished Clinical Trials

Some currently ongoing or unpublished trials that might influence this policy are listed in Table 9.

Table 9. Summary of Key Trials

NCT Number	Trial Name	Planned enrollment	Completion Date
Ongoing			
NCT04283227	OTL-200 in Patients With Late Juvenile Metachromatic Leukodystrophy (MLD)	6	Mar 2031
NCT03392987	A Safety and Efficacy Study of Cryopreserved OTL-200 for Treatment of Metachromatic Leukodystrophy	10	Jan 2026

NCT: national clinical trial.

Coding

Procedure codes on Medical Policy documents are included **only** as a general reference tool for each policy. **They may not be all-inclusive.**

The presence or absence of procedure, service, supply, or device codes in a Medical Policy document has no relevance for determination of benefit coverage for members or reimbursement for providers. **Only the written coverage position in a Medical Policy should be used for such determinations.**

Benefit coverage determinations based on written Medical Policy coverage positions must include review of the member's benefit contract or Summary Plan Description (SPD) for defined coverage vs. non-coverage, benefit exclusions, and benefit limitations such as dollar or duration caps.

CPT Codes	None
HCPCS Codes	J3391

*Current Procedural Terminology (CPT®) ©2024 American Medical Association: Chicago, IL.

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Centers for Medicare and Medicaid Services (CMS)

The information contained in this section is for informational purposes only. HCSC makes no representation as to the accuracy of this information. It is not to be used for claims adjudication for HCSC Plans.

The Centers for Medicare and Medicaid Services (CMS) does not have a national Medicare coverage position. Coverage may be subject to local carrier discretion.

A national coverage position for Medicare may have been developed since this medical policy document was written. See Medicare's National Coverage at <https://www.cms.hhs.gov>.

Policy History/Revision

Date	Description of Change
12/15/2025	Document updated with literature review. The following changes were made to Coverage: 1) Revised conditional criteria; and 2) Added "Atidarsagene autotemcel is considered experimental, investigational and/or unproven when the above criteria are not met." All new references were added with the exception of 33 and 36. Title changed from "Atidarsagene autotemcel".
08/15/2024	New medical document. Atidarsagene autotemcel (Lenmeldy™) may be considered medically necessary for the treatment of metachromatic leukodystrophy (MLD) if ALL the following criteria are met: individuals with disease onset at less than 7 years of age; AND documentation of an arylsulfatase A (ARSA) genotype consistent with pre-symptomatic late

	infantile (PSLI), OR pre-symptomatic early juvenile (PSEJ), OR early symptomatic early juvenile (ESEJ) metachromatic leukodystrophy; AND clinically stable and eligible to undergo hematopoietic stem cell (HSC) mobilization; AND individual does NOT have ANY of the following: late juvenile form of metachromatic leukodystrophy; positive for presence of Human Immunodeficiency Virus (HIV-1, HIV-2), Human T-lymphotrophic Virus (HTLV-1, HTLV-2), Hepatitis B Virus (HBV) or Hepatitis C Virus (HCV) or mycoplasma infection; history of prior gene therapy or allogeneic hematopoietic cell transplant (HCT). Repeat treatment of Atidarsagene autotemcel (Lenmeldy™) is considered experimental, investigational, and/or unproven. Atidarsagene autotemcel (Lenmeldy™) is considered experimental, investigational, and/or unproven for all other indications.