Atidarsagene Autotemcel for Metachromatic Leukodystrophy

Revised Background and Scope

April 6, 2023

Background

Metachromatic leukodystrophy (MLD) is a rare autosomal recessive genetic disorder that results in progressive loss of motor and cognitive function. The most common forms of MLD are typically rapidly fatal. The disease is caused by a mutation in the gene arylsulfatase-A (ARSA), which is required to break down sulfatide fats in the white matter of the brain, spinal cord, and peripheral nerves.[1 2] These accumulated fats cause the breakdown of the myelin sheath (i.e., demyelination), permanently damaging nerves and triggering deterioration of motor and cognitive function. Sulfatide fats can also accumulate outside the nervous system – in the gallbladder, for example, leading to acute biliary complications and possibly an increased risk of gallbladder cancer.[3]

Approximately one in 40,000 to 160,000 people are diagnosed with MLD across the world,[4] with an estimated 2,500 people living with MLD in the United States (US).[5] There is higher incidence of the disease among subgroups such as Habbanite Jews (1 in 75), western US Navajos (1 in 6,400), and Israeli Arabs (1 in 8,000).[4] The clinical subtypes of MLD are categorized by age of onset. The late infantile subtype is the most common and aggressive form of the disease, affecting 50-60% of MLD patients;[4] symptoms start before 30 months and patients lose the ability to swallow and walk within 1 – 2 years.[6] Median survival after onset of disease is around 8 years.[2] In the juvenile form, which occurs in 20-30% of MLD cases, symptoms start between 30 months – 6 years old (early juvenile) and 7 – 16 years old (late juvenile). Children with the early juvenile form also progress rapidly, with significant disability occurring within 3 years of symptom onset[6]; however, survival is longer than the late infantile type, up to 10 to 20 years.[2] The least common form is the adult type, which develops after 16 years of age. Adults with MLD have slower progression of symptoms and may live 20 to 30 years after diagnosis.[2]

MLD causes progressive neurological impairment, with symptoms dependent on the form of the disease. For example, in the late infantile form, children begin to miss or lose motor and cognitive milestones and can have low muscle tone, difficulty swallowing and speaking, and loss of vision. The juvenile form presents with difficulties in school due to behavioral and cognitive problems, as well as difficulty walking and loss of sensation. In adults, MLD manifests as behavioral and

psychiatric problems, which can lead to problems with work or school; drug or alcohol misuse are also common.[4] Because MLD patients either never achieve or progressively lose motor and cognitive functions (i.e., loss of walking and other physical abilities, loss of ability to communicate, and difficulty in swallowing, etc.), the caregiving impact for this disease is very high.[7] For example, caregivers spend an average of 15 hours per day caring for an affected child, affecting their mental and physical health, as well as their participation in the workforce, professional achievement, and personal relationships.[7]

Treatment for MLD is largely supportive, consisting of medications and procedures to treat symptoms such as seizures and difficulty swallowing, physical therapy and assistive devices for muscle spasticity, respiratory therapy and ventilation, and psychological and educational support for behavioral problems and learning disabilities.[1 2] Allogeneic hematopoietic stem cell transplant (HSCT) is sometimes offered as a treatment to attempt to slow down progression of disease, but it is uncertain what benefit it provides to late infantile or early juvenile MLD.[2 1] However, since there is currently no universal newborn screening for MLD, and diagnosis is often delayed due to lack of recognition of symptoms, many patients are diagnosed too late to even be considered for treatments other than supportive care.

Atidarsagene autotemcel (OTL-200 or "arsa-cel", brand name Libmeldy™ in Europe) is a gene therapy for MLD. The therapy works by delivering a lentiviral vector carrying a functional ARSA gene into the CD34+ cells that make white blood cells via hematopoietic stem and progenitor cells harvested from the patient (i.e., autologous HSCT). The treatment regimen also includes myeloablation of the bone marrow with busulfan prior to intravenous infusion with arsa-cel. Successful treatment results in supranormal expression of the ARSA enzyme.[8] The manufacturer, Orchard Therapeutics, is planning to submit the biologics license application (BLA) for arsa-cel in early 2023.[9]

Stakeholder Input

This revised scoping document was developed with input from diverse stakeholders, including caregivers of patients, clinicians, researchers, and the manufacturer of the agent of focus in this review. This document incorporates feedback gathered during preliminary calls with stakeholders and open input submissions from the public. In response to public comments, 1) we added further details about the severity of MLD to the background section; 2) we amended the inclusion criteria for arsa-cel to include GMFC-MLD score and IQ; 3) revised the time horizons in the comparative effectiveness analysis; and 4) added several patient-important outcomes. ICER looks forward to continued engagement with stakeholders throughout its review and encourages comments to refine our understanding of the clinical effectiveness and value of preventive treatments.

Caregivers (who are mainly parents) described many challenges associated with caring for children with MLD across the disease spectrum. Initial diagnosis can be challenging, particularly for the late infantile and early juvenile forms of the disease, as parents and clinicians may not recognize early symptoms. This leads to missed or delayed diagnosis, particularly since there is currently no universal newborn screening for this disease. Additionally, because the symptoms of MLD are more rapidly progressive in the late infantile and early juvenile forms of the disease, delays in diagnosis can affect a child's eligibility for treatment and clinical trials, as well as future family planning. Patient groups are advocating for and helping to develop newborn screening tests and programs.

As MLD progresses and children slowly lose motor and cognitive skills, the caregiving impact increases. Children with MLD typically have low motor tone and can have rigid muscles, so not only is it physically taxing to move the kids, but they also may require specialized equipment such as custom car seats, beds, wheelchairs, bath supports, and eventually oxygen, suction catheters, and ventilators. Additionally, families often need to modify their homes to accommodate the child's disabilities and obtain wheelchair vans. Since children with MLD may lose the ability to swallow, a gastrostomy tube (G-tube) and special diets may be required. During advanced stages of the disease, children may require home nursing care.

The impact of MLD on the family is tremendous, both in terms of caregiving and financially. Although many children with MLD qualify for governmental assistance in the form of county and state disability services, often one or both parents will still need to leave the workforce due to the intense caregiving needs. Since the disease is genetic, parents may have multiple affected children; unaffected children are impacted by the needs of affected sibling(s) as well. For example, travel can be very difficult given the amount of specialized equipment and number of accommodations needed to move the child. Furthermore, many of the home and car modifications needed are not covered by insurance. In fact, a study of the economic burden of rare diseases in the U.S. estimates that more than half of the costs incurred by the healthcare system are indirect non-medical costs absorbed directly by families living with rare disease.[10] Finally, regardless of whether the child is covered through commercial insurance or Medicaid (many children with MLD receive Medicaid), navigating insurance coverage can be time-consuming and frustrating due to the required authorizations, denials and appeals processes, and repetitive documentation submissions, with particular barriers related to obtaining coverage for nursing care, therapy, equipment, and out-of-network providers.[11]

Report Aim

This project will evaluate the health and economic outcomes for metachromatic leukodystrophy. The ICER value framework includes both quantitative and qualitative comparisons across treatments to ensure that the full range of benefits and harms – including those not typically captured in the clinical evidence such as innovation, public health effects, reduction in disparities, and unmet medical needs – are considered in the judgments about the clinical and economic value of the interventions.

Applicable Framework Adaptations

We propose to assess atidarsagene autotemcel (arsa-cel) under an adaptation of the ICER Value Framework for treatments of serious, ultra-rare conditions because we believe it meets the following criteria:

- The eligible patient populations for the treatment indication included in the scope of the ICER review is estimated at fewer than approximately 10,000 individuals.
- There are no ongoing or planned clinical trials of the treatment for a patient population greater than approximately 10,000 individuals.

We propose to assess atidarsagene autotemcel (arsa-cel) under an adaptation of the ICER Value Framework for treatments of high-impact "single and short-term therapies" (SSTs), because we believe they meet the following criteria defined as:

- The therapy is delivered through a single intervention or a short-term course (less than one year) of treatment that offers a significant potential for substantial and sustained health benefits extending throughout patients' lifetimes.
- The therapy can eradicate a disease or condition, or produce sustained major health gains that can halt the progression of significant illnesses.

Following formal public comment and discussions with stakeholders, ICER will make a final decision on whether the therapy meets these criteria and will be assessed using an adapted approach.

Scope of Clinical Evidence Review

The proposed scope for this assessment is described on the following pages using the PICOTS (Population, Intervention, Comparators, Outcomes, Timing, and Settings) framework. Evidence will be abstracted from all trials meeting our inclusion criteria, including randomized controlled trials, non-randomized trials, high-quality systematic reviews, and high-quality comparative cohort

studies. Our evidence review will include input from patients and patient advocacy organizations, data from regulatory documents, information submitted by manufacturers, and other grey literature when the evidence meets ICER standards (for more information, see ICER's grey literature policy).

All relevant evidence will be synthesized qualitatively or quantitatively. Wherever possible, we will seek out head-to-head studies of the interventions and comparators of interest. Data permitting, we will also consider combined use of direct and indirect evidence in network meta-analyses of selected outcomes. Full details regarding the literature search, screening strategy, data extraction, and evidence synthesis will be provided after the revised scope in a research protocol published on the Open Science Framework website (https://osf.io/7awvd/).

Populations

The populations of focus for this review are:

- Children with presymptomatic late infantile MLD
- Children with presymptomatic early juvenile MLD
- Children with early juvenile MLD who are early symptomatic (onset of symptoms before age seven) as defined by being able to ambulate independently (Gross Motor Function Classification for MLD [GFMC-MLD] score of ≤1) and with preserved cognition (intelligence quotient [IQ] score of ≥85).

Interventions

The intervention of interest for this review is atidarsagene autotemcel, "arsa-cel" (Libmeldy™, Orchard Therapeutics, EU), also known as OTL-200.

Comparators

We intend to compare arsa-cel to usual care, defined as supportive care that may include any non-disease modifying pharmacologic or non-pharmacologic treatment to manage the symptoms. Based on input from multiple experts, we do not expect to compare arsa-cel to HSCT, as in the above populations it is unclear that benefits of HSCT outweigh harms.

Outcomes

The outcomes of interest are described in the list below. Examples of relevant outcomes are drawn from an expert consensus document from The European Metachromatic Leukodystrophy initiative

(MLDi), which set forth to harmonize endpoints for an international disease registry for MLD,[12] as well as from input from caregivers.

- Patient-Important Outcomes
    - Overall survival
    - Motor function
        - Achievement of developmental milestones
        - Maintenance/loss of function (e.g, Gross Motor Function Measure, GFMC-MLD)
    - Cognitive function (e.g., Expressive Language Function Classification for MLD, IQ)
    - Behavioral outcomes
    - Need for ventilatory support
    - Pain
    - Positional comfort
    - Health-Related Quality of Life (e.g., EQ5D/5L, EQ5D-Y, HUI3, PedsQL)
    - Seizures
    - Peripheral neuropathy
    - Gallbladder disease
    - Engraftment
    - Caregiver impact (e.g., caregiver mental and physical health, quality of life)
    - Harms
        - Acute harms from bone marrow conditioning
            - Cytopenias
            - Infections
            - Death
            - Mucositis/stomatitis
            - Worsening of neurologic signs and symptoms
        - Late harms from gene therapy
            - Insertional oncogenesis
            - Long-term bone marrow abnormalities
        - Other serious adverse events
- Other Outcomes
    - Nerve function (e.g., nerve conduction velocity)
    - Brain imaging (e.g., total brain MRI score)
    - ARSA activity level
    - Urine sulfatide level
    - Anti-ARSA antibodies

Timing

Evidence on intervention effectiveness will be derived from studies of any duration.

Settings

All relevant settings will be considered, including inpatient and outpatient settings in the United States.

Potential Other Benefits and Contextual Considerations

Our reviews seek to provide information on potential other benefits offered by the intervention to the individual patient, caregivers, the delivery system, other patients, or the public that would not have been considered as part of the evidence on comparative clinical effectiveness. These general elements (i.e., not specific to a given disease) are listed in the table below.

Table 1. Categories of Contextual Considerations and Potential Other Benefits or Disadvantages

Contextual Consideration*
Acuity of need for treatment of individual patients based on short-term risk of death or progression to permanent disability
Magnitude of the lifetime impact on individual patients of the condition being treated
Other (as relevant)

*Contextual considerations refer to social or ethical priorities that shape to some extent how the value of any effective treatments for a particular condition will be judged.

Potential Other Benefit or Disadvantage*
Patients' ability to achieve major life goals related to education, work, or family life
Caregivers' quality of life and/or ability to achieve major life goals related to education, work, or family life
Patients' ability to manage and sustain treatment given the complexity of regimen
Society's goal of reducing health inequities
Other (as relevant)

*Potential other benefits or disadvantages are meant to reflect the broader effects of a specific treatment on patients, caregivers, and society.

Scope of Comparative Value Analyses

As a complement to the evidence review, we will develop an economic model to assess the lifetime cost-effectiveness of arsa-cel relative to usual care. The model structure will be based in part on a literature review of prior published models of MLD. The base case analysis will take a health care system perspective (i.e., focus on direct medical care costs only). Data permitting, productivity impacts and other indirect costs will be considered in a separate analysis. This modified societal perspective analysis will be considered as a co-base case when the societal costs of care are large relative to direct health care costs, and the impact of treatment on these costs is substantial. This will most often occur in cases where the incremental cost-effectiveness ratio changes by greater than 20%, greater than $200,000 per QALY, and/or when the result crosses the threshold of $100,000-$150,000 per QALY gained. The target population will consist of infants and children with presymptomatic late infantile MLD and presymptomatic or early symptomatic early juvenile MLD. The model will consist of health states based on the Gross Motor Function Classification. A cohort of patients will progress through health states over a lifetime time horizon, modeling patients from treatment initiation until death. In addition, cost-effectiveness will be estimated for shorter time horizons should there be clinical or economic rationale to do so.

Key model inputs will include clinical probabilities, quality of life values, and health care costs. Probabilities, costs, and other inputs will differ to reflect varying effectiveness between interventions. Treatment effectiveness will be estimated using data from relevant clinical trials, data on the natural history of MLD, and the clinical evidence review.

Health outcomes and costs will be dependent on time spent in each health state, clinical events, adverse events (AEs), and direct medical costs. The health outcome of each intervention will be evaluated in terms of clinical outcomes related to developmental milestones, life-years gained, quality-adjusted life years (QALYs) gained, and equal value of life years gained (evLYG). Quality of life weights will be applied to each health state, including quality of life decrements for serious adverse events. The model will include direct medical costs, including but not limited to costs related to drug administration, condition-related care, and serious adverse events. In addition, productivity changes and other indirect costs will be included in a separate analysis if available data allow. Results will be expressed in terms of the marginal cost per QALY gained, cost per evLYG, cost per life-year gained.

In separate analyses, we will explore the potential health care system budgetary impact of treatment over a five-year time horizon, utilizing published or otherwise publicly-available information on the potential population eligible for treatment and results from the economic model for treatment costs and cost offsets. This budgetary impact analysis will indicate the relation between treatment prices and level of use for a given potential budget impact, and will allow

assessment of any need for managing the cost of such interventions. More information on ICER's methods for estimating potential budget impact can be found here.

Identification of Low-Value Services

ICER includes in its reports information on wasteful or lower-value services in the same clinical area that could be reduced or eliminated to create additional resources in health care budgets for higher-value innovative services (for more information, see ICER's Value Assessment Framework). These services are ones that would not be directly affected by arsa-cel (e.g., reduced need for nutritional support), as these services will be captured in the economic model. Rather, we are seeking services used in the current management of MLD beyond the potential offsets that arise from a new intervention. ICER encourages all stakeholders to suggest services (including treatments and mechanisms of care) that could be reduced, eliminated, or made more efficient.

References

1. Shaimardanova AA, Chulpanova DS, Solovyeva VV, et al. Metachromatic Leukodystrophy: Diagnosis, Modeling, and Treatment Approaches. *Frontiers in medicine.* 2020;7:576221-576221.
2. van Rappard DF, Boelens JJ, Wolf NI. Metachromatic leukodystrophy: Disease spectrum and approaches for treatment. *Best Pract Res Clin Endocrinol Metab.* 2015;29(2):261-273.
3. Kim J, Sun Z, Ezekian B, et al. Gallbladder abnormalities in children with metachromatic leukodystrophy. *J Surg Res.* 2017;208:187-191.
4. Gomez-Ospina N. Arylsulfatase A Deficiency. In: Adam MP, Everman DB, Mirzaa GM, et al., eds. *GeneReviews(®).* Seattle (WA): University of Washington, Seattle Copyright © 1993-2023, University of Washington, Seattle. GeneReviews is a registered trademark of the University of Washington, Seattle. All rights reserved.; 2006 [Updated 2020].
5. MLD Foundation. Analysis of MLD Incidence & Prevalence: Domestic & Worldwide. www.mldfoundation.org. Published 2017. Updated February 2022. Accessed April 4, 2023.
6. Fumagalli F, Zambon AA, Rancoita PMV, et al. Metachromatic leukodystrophy: A single-center longitudinal study of 45 patients. *J Inherit Metab Dis.* 2021;44(5):1151-1164.
7. Sevin C, Barth M, Wilds A, et al. An international study of caregiver-reported burden and quality of life in metachromatic leukodystrophy. *Orphanet J Rare Dis.* 2022;17(1):329.
8. Fumagalli F, Calbi V, Natali Sora MG, et al. Lentiviral haematopoietic stem-cell gene therapy for early-onset metachromatic leukodystrophy: long-term results from a non-randomised, open-label, phase 1/2 trial and expanded access. *Lancet.* 2022;399(10322):372-383.
9. Orchard Therapeutics Highlights Recent Progress Across HSC Gene Therapy Portfolio and Outlines Key 2023 Milestones [press release]. January 9, 2023 2023.
10. EveryLife Foundation for Rare Diseases. The National Economic Burden of Rare Disease Study. 2021.
11. Pasquini TLS, Goff SL, Whitehill JM. Navigating the U.S. health insurance landscape for children with rare diseases: a qualitative study of parents' experiences. *Orphanet J Rare Dis.* 2021;16(1):313.
12. Schoenmakers DH, Beerepoot S, van den Berg S, et al. Modified Delphi procedure-based expert consensus on endpoints for an international disease registry for Metachromatic Leukodystrophy: The European Metachromatic Leukodystrophy initiative (MLDi). *Orphanet J Rare Dis.* 2022;17(1):48.