REPORT AT A GLANCE: METACHROMATIC LEUKODYSTROPHY (MLD)

OCTOBER 2023

KEY FINDINGS

Intervention	Evidence Rating	Annual WAC*	Health-Benefit Price Benchmark	Change from Annual Price to Reach Threshold Price
atidarsagene autotemcel ("arsa-cel", Orchard Therapeutics)	Presymptomatic late infantile and early juvenile MLD ("A") Early symptomatic, early juvenile MLD (B+)	Placeholder price: $2,800,240	$2.3M to $3.9M	Not applicable

"MLD is a devastating disease for children and their caregivers. It is extremely rare, and most doctors have never seen a case. We again see a gene therapy potentially filling the promise of treating a disease that was previously untreatable, delivering remarkable clinical benefits and extending life. If the manufacturer prices arsa-cel in line with its price in Europe, despite being very expensive, arsa-cel would be cost-effective."

– ICER's Chief Medical Officer, David Rind, MD

THEMES AND RECOMMENDATIONS

- In the context of a rapidly progressive disease such as MLD, when a treatment has a high likelihood of being approved by the FDA, payers should be evaluating evidence and preparing policies in advance to avoid a new-to-market block on insurance coverage.
- Payers should cover fertility preservation in concert with coverage of gene therapies.
- Manufacturers should actively engage with independent value assessment efforts to allow public dialogue on access and fair pricing with broad input from patients and other stakeholders. Orchard Therapeutics has set a good example for other developers of transformative gene therapies.

Clinical Analyses

KEY CLINICAL BENEFITS STUDIED IN CLINICAL TRIALS

Metachromatic leukodystrophy (MLD) is a rare autosomal recessive genetic disorder that results in progressive loss of motor and cognitive function. It is caused by mutations in the arylsulfatase-A (*ARSA*) gene affecting the production of the enzyme ARSA; it is sometimes also caused by mutations in *PSAP* genes. Although exact prevalence is difficult to ascertain, it is estimated that one in 40,000 to 160,000 people are diagnosed with MLD across the world. The clinical subtypes of MLD are categorized by age of onset. The late infantile subtype (LI-MLD) is the most common (50-60% of patients) and aggressive form of the disease; symptoms start before 30 months and children lose the ability to walk and swallow within 1-2 years. In the early juvenile form (EJ-MLD), symptoms start between 30 months and six years of age, and significant disability occurs within three years of symptom onset.

Early symptoms of LI- and EJ-MLD may include low motor tone, losing or not achieving motor and cognitive milestones, and difficulties in school due to behavioral and cognitive problems. As the disease progresses, children develop difficulty swallowing and breathing, and eventually may require gastrostomy tubes, suctioning, and ventilatory support. Mean survival varies based on subtype, with LI-MLD children surviving around eight years and those with EJ-MLD 10-20 years. Because MLD patients either never achieve or progressively lose motor and cognitive functions, the caregiving impact for this disease is very high; caregivers described the need to spend an average of 15 hours per day caring for an affected child. Current treatment for MLD is largely supportive. Allogeneic hematopoietic stem cell transplant (HSCT) is sometimes offered as in an attempt to slow progression, but it is uncertain what benefit it provides in LI- and EJ-MLD.

Atidarsagene autotemcel (OTL-200 or "arsa-cel", brand name Libmeldy™ in Europe) is a gene therapy for MLD. It involves autologous stem-cell transplant, retrieving stem and progenitor cells from the child's blood, inserting functional *ARSA* genes into CD34+ cells outside the body using a lentiviral vector, and reinfusing these treated cells. Treatment requires myeloablation of the bone marrow with busulfan prior to reinfusion of cells. The manufacturer, Orchard Therapeutics, submitted a biologics license application (BLA) to the US Food and Drug Administration for arsa-cel in mid-2023, with a decision expected by March 18, 2024.

We reviewed the clinical effectiveness of arsa-cel for the treatment of presymptomatic LI-MLD, presymptomatic EJ-MLD, and early symptomatic EJ-MLD compared to usual care. Results from the 39 patients who participated in two key clinical trials (Phase I/II study and Phase II single-arm, open-label trials conducted in Milan, Italy) and expanded access frameworks and compassionate use programs show that treatment with arsa-cel resulted in ARSA levels in the normal or supranormal range and preservation of motor and cognitive function compared with natural history controls, and also increased survival in the presymptomatic LI- and EJ-MLD populations. In the early symptomatic EJ-MLD population, cognitive function was preserved in the majority of patients and there was a trend towards preservation of motor function, and greater severe motor-impairment free survival compared with natural history controls. Durability of effect and long-term harms are uncertain.

Given that the early onset forms of MLD are rapidly progressive and fatal, and the majority of presymptomatic LI and EJ-MLD patients who underwent arsa-cel therapy remained either asymptomatic or with mild symptoms, we conclude

Clinical Analyses

that in children with presymptomatic LI-MLD and presymptomatic EJ-MLD, we have high certainty of a substantial net health benefit ("A").

The magnitude of benefit and certainty in that benefit are both smaller for treatment of children with early symptomatic EJ-MLD. These children will not return to normal health, treatment with busulfan carries a risk of death, and long-term outcomes are less certain. Additionally, clinical experts, based on experience in patients treated with hematopoietic stem cell therapy, were concenerd that, in some patients, treatment with arsa-cel may carry the risk of hastening progression of physical and cognitive decline before stabilization. occurs. Given these uncertainties, in children with early symptomatic EJ-MLD, we have moderate certainty of a small or substantial net health benefit with high certainty of at least a small net health benefit ("B+"). However, families for whom the possible risk of initial faster progression after treatment with arsa-cel is determinative may reasonably conclude that current evidence is insufficient.

Economic Analyses

LONG-TERM COST EFFECTIVENESS

We developed a lifetime semi-Markov model of MLD that assumed disease stabilization for at least 12 years after successful treatment. The cost-effectiveness of arsa-cel varies depending on the subtype treated. Assuming a single price, the Health Benefit Price Benchmark (HBPB) for arsa-cel ranges from $2,294,000 to $3,940,000. The actual cost-effectiveness of arsa-cel will depend on its price and its long-term durability.

POTENTIAL BUDGET IMPACT

At the placeholder price of $2,800,240 per treatment course for arsa-cel (to be paid up front), 100% of patients (N=14 patients per year) could be treated over the span of five years without crossing the ICER budget impact threshold of $777 million per year.

ICER is not issuing an access and affordability alert for arsa-cel. The actual price of arsa-cel is unknown. However, using the placeholder price of $2,800,240 per treatment course, all eligible patients could be treated within five years without reaching the ICER potential budget impact threshold of $777 million per year.

Public Meeting Deliberations

VOTING RESULTS

For children with presymptomatic late infantile MLD:

- All panelists (13-0) found that current evidence is **adequate** to demonstrate a net health benefit for atidarsagene autotemcel (arsa-cel) when compared to usual care.

For children with presymptomatic early juvenile MLD:

- All panelists (13-0) found that current evidence is **adequate** to demonstrate a net health benefit for atidarsagene autotemcel (arsa-cel) when compared to usual care.

For children with symptomatic early juvenile MLD:

- A majority of panelists (12-1) found that current evidence is **adequate** to demonstrate a net health benefit for atidarsagene autotemcel (arsa-cel) when compared to usual care.

For children with presymptomatic late infantile MLD or presymptomatic early juvenile MLD, panel members also weighed potential benefits and disadvantages beyond the direct health effects and broader contextual considerations. Voting highlighted the following as particularly important for payers and other policymakers to note:

- The acuity of need for treatment of individual patients based on short-term risk of death or progression to permanent disability;
- The magnitude of the lifetime impact on individual patients of MLD;
- The likelihood that these new treatments will improve patients' broader ability to achieve major life goals related to education, work, or family life;
- The likelihood that these new treatments will improve caregivers' quality of life and/or ability to achieve major life goals related to education, work, or family life.

Consistent with ICER's process, because there is no firm estimate yet of a potential launch price for the treatment, the panel did not take separate votes on the treatments' long-term value for money.

About ICER

The Institute for Clinical and Economic Review (ICER) is an independent nonprofit research institute that produces reports analyzing the evidence on the effectiveness and value of drugs and other medical services. ICER's reports include evidence-based calculations of prices for new drugs that accurately reflect the degree of improvement expected in long-term patient outcomes, while also highlighting price levels that might contribute to unaffordable short-term cost growth for the overall health care system.

ICER's reports incorporate extensive input from all stakeholders and are the subject of public hearings through three core programs: the California Technology Assessment Forum (CTAF), the Midwest Comparative Effectiveness Public Advisory Council (Midwest CEPAC) and the New England Comparative Effectiveness Public Advisory Council (New England CEPAC). These independent panels review ICER's reports at public meetings to deliberate on the evidence and develop recommendations for how patients, clinicians, insurers, and policymakers can improve the quality and value of health care.

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