Atidarsagene Autotemcel for Metachromatic Leukodystrophy

Final Evidence Report

October 30, 2023

Prepared for

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Grace Lin served as the lead author for the report. Shahariar Mohammed Fahim, Belen Herce-Hagiwara, and Finn Raymond led the systematic review and authorship of the comparative clinical effectiveness section of this report. Josh J. Carlson and Kangho Suh developed the cost-effectiveness model and authored the corresponding sections of the report with assistance from Ronald Dickerson. Marina Richardson provided consultation on the cost-effectiveness analyses and

conducted analyses for the budget impact model. David M. Rind and Steven D. Pearson provided methodologic guidance on the clinical and economic evaluations. We would also like to thank Kelsey Gosselin and Yasmine Kayali for their contributions to this report.

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In the development of this report, ICER's researchers consulted with clinical experts, patients, manufacturers, and other stakeholders. The following individuals served as external reviewers of the draft evidence report:

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No relevant conflicts of interest to disclose, defined as more than $10,000 in healthcare company stock or more than $5,000 in honoraria or consultancies during the previous year from health care manufacturers or insurers.

None of the external reviewers or other experts we spoke to are responsible for the final contents of this report, nor should it be assumed that they support any part of it. Furthermore, it is possible that external reviewers may not have had the opportunity to review all portions of this draft report. The report should be viewed as attributable solely to the ICER team and its affiliated researchers.

To protect patient confidentiality, ICER does not routinely name individual patients or care partners who provided us with input and feedback.

For a list of stakeholders from who we requested input from, or who have submitted public comments so far, please visit: https://icer.org/wp-content/uploads/2023/07/ICER_MLD_Revised-Key-Stakeholders-List_For-Publication_07262023.pdf

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List of Acronyms and Abbreviations Used in this Report

AHRQ	Agency for Healthcare Research and Quality
ARSA	Arylsulfatase A
CI	Confidence interval
CUPs	Compassionate use programs
DQp	Development quotient performance score
EAFs	Expanded-access frameworks
EJ	Early juvenile
ES	Early symptomatic
evLY	Equal value of life years
FINOSE	Finland, Norway, and Sweden
GMFC	Gross Motor Function Classification
GMFM	Gross Motor Function Measure
HBPB	Health benefit price benchmark
HRQoL	Health-related quality of life
HSCT	Hematopoietic stem cell transplant
HTA	Health technology assessment
IQ	Intelligence quotient
LI	Late infantile
ML	Milliliter
MLD	Metachromatic leukodystrophy
MRI	Magnetic resonance imaging
N	Total number
NICE	National Institute for Health and Care Excellence
NR	Not reported
PBI	Potential budget impact
PBMC	Peripheral blood mononuclear cells
PICOTS	Populations, Intervention, Comparators, Outcomes, Timing, Settings
PS	Pre-symptomatic
PSS	Performance standard score
QALY	Quality-adjusted life year
SD	Standard deviation
UK	United Kingdom
US	United States
WAC	Wholesale acquisition cost

Executive Summary

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, the worldwide incidence is estimated to be one in 40,000 to 160,000 live births.[1] 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;[1] symptoms start before 30 months and children lose the ability to walk and swallow within 1-2 years.[2] 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.[2]

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.[2,3] 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.[4] Current treatment for MLD is largely supportive.[5 3] 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.[3 5]

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.[6] 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.[7]

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. For all three groups, short-term harms were primarily due to busulfan conditioning, including febrile neutropenia and stomatitis during the pre-treatment and treatment phases. 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 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 concerned 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.

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.

Appraisal committee votes on questions of comparative effectiveness along with policy recommendations regarding pricing, access, and future research are included in the Report. Several key themes are highlighted below:

- Given that treatment is most effective in the presymptomatic phase, newborn screening will be important in identifying children before symptoms of MLD appear. Policymakers and leaders who manage state and federal procedures governing universal newborn screening should prepare to be able to offer testing for MLD as soon as the test is available.
- 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.

1. Background

Metachromatic leukodystrophy (MLD) is a rare autosomal recessive genetic disorder that results in progressive loss of motor and cognitive function. Although exact prevalence is difficult to ascertain, it is estimated that the worldwide incidence is one in 40,000 to 160,000 live births.[1] There are an estimated 2,500 people living with MLD in the United States (US).[8] The disease is caused by one of over 250 mutations in the *ARSA* gene that codes for the enzyme arylsulfatase-A (ARSA), or rarely the *PSAP* gene that codes for saposin B, which activates ARSA.[5,9] Both ARSA and saposin B are required to break down sulfatide fats in the myelin forming cells (oligodendrocytes and Schwann cells) of the central and peripheral nervous system, respectively.[5 3] In MLD, as sulfatide fats accumulate, they cause breakdown of the myelin sheath (i.e., demyelination), permanently damaging nerves and triggering a secondary neurodegenerative process, leading to deterioration of motor and cognitive function. Sulfatide fats can also accumulate outside the nervous system; in the gallbladder, accumulation of sulfatides cause gallbladder thickening, biliary sludge, polyp formation and subsequent acute biliary complications and/or an increased risk of gallbladder cancer.[10]

The clinical subtypes of MLD are categorized by age of onset. The late infantile subtype (LI-MLD) is the most common and aggressive form of the disease, affecting 50-60% of MLD patients.[1] Symptoms start before 30 months, with patients losing the ability to walk (or fail to start walking) within 1 – 2 years. Patients subsequently lose the ability to communicate, have decline in cognitive function, and eventually lose the ability to swallow.[11] Patients with LI-MLD typically survive fewer than eight years after onset of symptoms.[2 3] In the juvenile form, which occurs in 20-30% of MLD cases, symptoms start between 30 months – 6 years old (early juvenile or EJ-MLD) and 7 – 16 years old (late juvenile). Cognitive symptoms such as learning disabilities and behavioral issues are more prominent in this form of MLD.[12] Children with the juvenile forms of MLD can also progress rapidly, particularly after loss of independent ambulation, with significant disability generally occurring within three years of symptom onset;[2] however, survival is somewhat longer than the late infantile type, typically 10-20 years from onset of symptoms.[2,3] Delays in diagnosis and misdiagnosis are common in children without a diagnosed sibling, with a the time from first symptom to diagnosis of four months to one year with LI-MLD and up to seven years for children with juvenile MLD.[12]

Because LI and EJ-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, seizures, etc.), quality of life for MLD patients is severely impacted as the disease progresses and the caregiving impact for this disease is very high.[4,13,14] For example, caregivers reported an average of 30 outpatients visits and nearly three inpatient hospital visits in the previous 12 months, as well as more difficulties doing usual activities and higher rates of anxiety and depression than the general US population.[4] In later stages of the disease, as children lose mobility and may require feeding tubes and ventilators, caregiving impact increases and the

majority of caregivers report a negative impact of the disease on familial relationships, social activities, employment status, professional achievement, and leisure activities. Overall, caregivers may spend an average of 15 hours per day caring for an affected child in addition to any nursing assistance.[4]

Treatment for MLD is largely supportive, consisting of medications and procedures to treat symptoms such as seizures, muscle spasticity, pain, 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.[5 3] 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.[3 5] However, since newborn screening for MLD has not been widely implemented, many patients are diagnosed too late to be considered for treatments other than supportive care.

Atidarsagene autotemcel (OTL-200 or "arsa-cel", brand name Libmeldy™ in Europe) is a one-time gene therapy for MLD caused by mutations in the *ARSA* gene. The therapy involves an autologous stem-cell transplant process. First, hematopoietic stem and progenitor cells are harvested from the patient. The cells are then sent to the manufacturer and CD34+ cells are then transduced with a lentiviral vector carrying a functional *ARSA* gene; cryopreserved cells are then shipped back to the treatment center. After a myeloablative conditioning regimen with busulfan, the cells are then delivered via intravenous infusion. Once the cells have engrafted, the CD34+ cells repopulate the bone marrow, giving rise to peripheral blood mononuclear cells (PBMCs) that can produce the normal to supranormal levels of ARSA enzyme.[6] The manufacturer, Orchard Therapeutics, submitted a biologics license application (BLA) to the US Food and Drug Administration (FDA) for arsa-cel in mid-2023, with a decision expected by March 18, 2024.[7]

Table 1.1. Interventions of Interest

Intervention	Mechanism of Action	Delivery Route	Prescribing Information
Atidarsagene autotemcel (arsa-cel)	CD34+ autologous hematopoietic stem cells using an ARSA-expressing lentiviral vector	Intravenous infusion following myeloablative conditioning with chemotherapy	Minimum dose of 3×10^6 CD34+ cells/kg of body weight

ARSA: arylsulfatase A, kg: kilogram

2. Patient and Caregiver Perspectives

This report was developed with input from diverse stakeholders, including caregivers of patients, clinicians, researchers, and the manufacturer of the agent of focus in this review. It incorporates feedback gathered during calls with stakeholders and open input submissions from the public. 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 were mainly parents of children with MLD) described many challenges associated with caring for children with MLD across the disease spectrum. Initial diagnosis was often challenging, particularly for the late infantile and early juvenile forms of the disease, as parents and clinicians did not recognize early symptoms as part of MLD. This led to incorrect and delayed diagnoses in many cases and affected a child's eligibility for treatment and clinical trials, as well as future family planning. Children with a sibling with MLD may be able to be diagnosed before MLD symptoms start; however, without newborn screening, most children will not come to attention prior to the onset of symptoms. With the emergence of arsa-cel as a potentially effective treatment, the identification of all LI and juvenile patients at birth through newborn screening is a key focus of patient advocacy to optimize potential therapeutic benefits of treatment by moving the early symptomatic population to presymptomatic.

As MLD progresses and children lose motor and cognitive skills, the caregiving impact increases. Parents described how physically taxing it was to move the children with MLD due to both low muscle tone and stiffness of the body and caused them to need specialized equipment such as custom car seats, beds, wheelchairs, and bath supports to assist with transfers/transport and to keep children comfortable. In addition, parents discussed how regular physical and occupational therapy were important to help children maintain as much strength, mobility, and function for as long as possible. As the disease progressed, families often needed to modify their homes to accommodate the child's disabilities and needed to obtain wheelchair vans. Children who lost the ability to swallow required a gastrostomy tube (G-tube) for hydration, medications, and nutrition and parents reported inadequate training of caregivers in G-tube management. For children of school age, parents described how cognitive and mobility difficulties resulted in the need for individualized education plans and additional assistance at school. Although some children were too fragile to attend school, those that did gain benefit from the social contact with their peers. During advanced stages of the disease, parents described needing to use suction catheters, oscillation vests, cough assists, and eventually ventilators to help their children breathe. For ventilator-dependent children, families effectively needed to set up an intensive care unit within the home; caregivers felt that they did not have adequate training or preparation for this level of care. Additionally, this level of care could be ongoing for years, depending on disease course and

family preferences. Furthermore, the COVID-19 pandemic and nursing shortages highlighted the ongoing difficulties MLD families have accessing the specialized nursing care that children with late-stage MLD require. Caregiving caused physical and mental consequences for caregivers as well. For example, parents described developing back pain and hernias from lifting children, as well as anxiety both about current child health and future disease progression.

MLD has an enormous impact on the family. The long-term stresses can cause interpersonal relationship challenges that may lead to separation and divorce. Since the disease is genetic, parents may have multiple affected children and/or may face decisions about their plans for future children. Unaffected children are also impacted by the needs of affected sibling(s). For example, parents described missing events for their other child(ren) due to the caregiving needs of a child with MLD. Siblings also missed out on events outside of the home due to the affected child's caregiving needs or need to quarantine during COVID-19. Travel was difficult given the amount of specialized equipment and number of accommodations needed to move the child, and thus family trips were limited. Finally, families who lived far from centers offering HSCT or gene therapy often had to spend months away from home and possibly living apart from other family members, leaving their jobs, and/or needing to find childcare for their other children during treatment.

There is a large financial impact from MLD. Although many children with MLD qualify for governmental assistance in the form of county and state disability services, one or both parents often needed to leave the workforce. Many of the home and car modifications needed are not covered by insurance. Medicaid programs vary in their coverage of services and some parents were advised to move to states with more generous Medicaid benefits. Regardless of whether the child was covered through Medicaid or commercial insurance, navigating insurance coverage was 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, and equipment. Some parents reported that delays in care due to insurance problems may have led to worse outcomes for their children.

We spoke with families whose children had been treated with arsa-cel. They expressed that they were grateful for the opportunity for an effective treatment for their child; however, the process and cost of gene therapy were tremendous. Since arsa-cel is not yet approved in the US, families needed to raise money to travel to Italy to participate in the clinical trial and spent months apart from other family members while their children were undergoing treatment. Parents also raised concerns about gene therapy, including progression of disease while waiting for cell prep and growth, undergoing chemotherapy, and waiting for engraftment, as well as future infertility from chemotherapy, and the long-term risk of cancer. Nevertheless, parents were hopeful that gene therapy would provide their children with more normal lives.

Concerns about access to care and potential inequities of treatment were raised. Families who lived in rural areas, far from specialized centers, described having to travel long distances for

appointments and to receive treatment. The potential expense of gene therapy and whether insurance would cover the procedure were raised as particular concerns for socioeconomically disadvantaged families. Finally, patient groups felt that lack of access to an effective treatment should be considered an additional harm to patients and families, since those patients would be denied the potential benefits of treatment, namely to live longer lives with less disability.

3. Comparative Clinical Effectiveness

3.1. Methods Overview

Detailed methods for the systematic literature review assessing the evidence on arsa-cel for the treatment of MLD are available in Supplement Section D1.

Scope of Review

We reviewed the clinical effectiveness of arsa-cel for the treatment of MLD compared to usual care, defined as supportive care that may include any non-disease modifying pharmacologic or non-pharmacologic treatment to manage symptoms. We sought evidence on patient important outcomes including overall survival, motor function, cognitive function, behavioral outcomes, health-related quality of life, acute harms from bone marrow conditioning and late harms from gene therapy. The full scope of the review is available in Supplement Section D1.

Evidence Base

A total of five references from two clinical trials of arsa-cel met our inclusion criteria. Detailed study design of the trials can be found in Table 3.1 and in Supplement Table D3.1. Although we reviewed data from all published studies and presentations, in this report, we focus on the integrated data provided by the manufacturer, as this data set includes data from the clinical trials, expanded access frameworks, and compassionate use programs, and are the most recent data available.

Trial Inclusion and Exclusion Criteria

Arsa-cel was studied in two key clinical trials, a Phase I/II study and a Phase II study. Both were single-arm, open-label studies conducted in Milan, Italy. In both studies, children had to have a diagnosis of MLD confirmed by biochemical and molecular testing. The Phase I/II study included children with disease onset younger than age seven years old with pre-symptomatic LI-MLD, pre-symptomatic EJ-MLD, and early symptomatic EJ-MLD.[15] Because the study was focused on LI and EJ-MLD, participants either had to have an older sibling with MLD whose symptoms appeared prior to seven years of age, or had to have testing that strongly suggested LI or EJ-MLD.[16] The original protocol defined early symptomatic EJ-MLD as an intelligence quotient (IQ) of ≥70 and the ability to take ≥10 steps independently;[6] however, a post-hoc analysis of treatment failures done during the evaluation process of arsa-cel 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.[17]

In both Phase I/II and Phase II studies, children with MLD who went through allogenic HSCT and had evidence of residual cells of donor origin were excluded.[15,16] Other notable exclusion criteria in the Phase II study included delay in achieving independent standing or walking with abnormal signs at neurological evaluation as well as documented cognitive, motor, or behavioral functional impairment for children with LI-MLD and Gross Motor Function Classification (GMFC-MLD) level ≥2 or cognitive impairment as defined by an IQ<85 for children with EJ-MLD.[16] See Supplement Section A1 for details on GMFC levels.

After the Phase I/II study closed the enrollment, additional participants were also recruited through expanded-access frameworks (EAFs) and compassionate use programs (CUPs) in between the Phase I/II and Phase II study.[6,18] The integrated data submitted by the manufacturer includes data from all sources – the two clinical studies as well as expanded access frameworks and compassionate use programs.

Table 3.1. Overview of Key Studies

Trials	N	Population	Key Outcomes
Phase I/II	20	Children with disease onset at less than 7 years of age with pre-symptomatic late infantile, presymptomatic early juvenile, or early symptomatic early juvenile MLD.	• Improvement of Gross Motor Function Measure (GMFM-88) compared to natural history cohort • Increase in ARSA Activity compared to baseline
Phase II	10	Children with disease onset at less than 7 years of age with presymptomatic late infantile, presymptomatic early juvenile, or early symptomatic early juvenile MLD.	• Increase in Gross Motor Function Measure (GMFM-88) compared to natural history cohort
Expanded Access Frameworks (EAFs)	3	Early onset MLD patients with similar enrollment criteria	• Similar endpoints to those in the primary study
Compassionate Use Programs (CUPs)	6		

ARSA: arylsulfatase A, CUPs: Compassionate Use Programs, EAFs: Expanded Access Frameworks, GMFM: gross motor function measure, MLD: metachromatic leukodystrophy, N: total number

Key Trial Characteristics and Outcomes

In both the Phase I/II and Phase II studies, a submyeloablative or myeloablative busulfan conditioning regimen was administered prior to the IV infusion of arsa-cel.[6,18] The Phase I/II study used a fresh formulation of arsa-cel while the Phase II study used a cryopreserved (i.e., frozen transduced progenitor cells) formulation.[19] The Phase I/II trial had co-primary outcomes of a ≥10% improvement in Gross Motor Function Measure (GMFM-88) total score compared to a MLD natural history cohort at 24 months and change from baseline ARSA activity in peripheral blood mononuclear cells (PBMC) at 24 months.[6] The primary outcome for the Phase II trial was change in

GMFM-88 score at 24 months while change in ARSA activity level was assessed as a secondary outcome.[16] Other secondary endpoints measured in both trials included change in Gross Motor Function Classification (GMFC-MLD) score, change in cognition (IQ, Development Quotient Performance [DQp] score), change in nerve conduction velocity, change in total score for brain magnetic resonance imaging (MRI), busulfan related harms, and gene-therapy related harms.[15,16] The protocols in the expanded-access framework and compassionate use program were similar.[6] See Supplement Section A1 for more detailed definitions of the GMFM and GMFC-MLD outcomes.

Participant Baseline Characteristics

A total of 39 MLD patients (19 presymptomatic LI-MLD, 8 presymptomatic EJ-MLD, 12 early symptomatic EJ-MLD) were treated using arsa-cel in Phase I/II study (n=20), Phase II study (n=10), EAFs (n=3), and CUPs (n=6). However, two patients (one LI-MLD patient who was symptomatic and one early symptomatic EJ-MLD patient who had progressive symptoms of MLD) were excluded since they were treated prior to a major protocol revision. Thus, only 37 treated patients were included in an integrated efficacy analysis.[18] Additionally, two early symptomatic EJ-MLD patients were excluded from the analyses provided to ICER by the manufacturer because these patients did not meet the criteria of IQ≥85 and GMFC<1 in the label for Libmeldy and thus would not be eligible to be treated in clinical practice.[17] One of those patients had substantial cognitive decline at baseline and the other had rapid progression beyond GMFC-MLD level 1 between screening and initiation of treatment; both patients died due to disease progression. The treated cohort (n=35) was then compared to 43 MLD patients (26 LI-MLD, 17 EJ-MLD) from a subset of a natural history cohort study conducted in Milan, Italy between 2000 and 2017.[18, 1] Table 3.2 shows the baseline characteristics of 35 arsa-cel treated MLD patients and 43 natural history patients.

The participants in both studies and the natural history cohort were predominately male and white. Median age at first contact or gene therapy was much younger than the predicted age of symptom onset for the pre-symptomatic LI-MLD and EJ-MLD groups (10 months at gene therapy versus 18 months predicted age of symptom onset for LI-MLD and 16 months at gene therapy versus 45 months predicted age of symptom onset for presymptomatic EJ-MLD). For early symptomatic EJ-MLD patients, median onset of symptoms was around 64 months and median age at gene therapy was 67 months. The natural history cohort included slightly older LI-MLD patients, with a median age of 19 months, and slightly younger EJ-MLD patients, with a median age of 53 months. The arsa-cel treated LI-MLD patients were followed for a median of six years and up to 11 years. Both pre-symptomatic and early symptomatic EJ-MLD patients treated with arsa-cel were followed for a median of three and seven years, respectively, and up to nine years. The LI-MLD patients in the natural history cohort were followed for a median of 4.4 years, while the EJ-MLD patients in the natural history cohort were followed for a median of 5.6 years and up to 20 years.[17] See Table 3.2 below and Supplement Table D3.2.

GMFM-88 was used to measure the changes in gross motor function over time. The GMFM-88 measures gross motor function in five domains: lying and rolling; sitting, crawling and kneeling; standing; and walking, running and jumping. Scores range from 0 to 100 with a higher score indicating better performance. It is important to note that the normal range of GMFM-88 differs according to chronological age of the child. The mean baseline GMFM-88 score for arsa-cel treated pre-symptomatic LI-MLD patients was 47.2 (SD 21.22), which is considered in the normal range; for pre-symptomatic EJ-MLD patients the mean score was 72.04 (SD 18.11) and for early symptomatic EJ-MLD patients, the mean score was 92.4 (SD 6.69). No baseline data on GMFM-88 was presented for the natural history cohort participants because they were recruited at different stages of disease and thus a mean baseline GMFM-88 score would not be meaningful.[17]

The median ARSA activity level in PBMC was around 26 nmol/mg/h at baseline for all three subtypes of MLD treated with arsa-cel (reference range 38.8 to 218.5 nmol/mg/h). For patients in the natural history cohort, ARSA activity levels were recorded at diagnosis in leukocytes (N=42) and PBMC (N=1). All ARSA levels were well below the normal range of the lab that measured it.[17] Details about the baseline characteristics of both treated and untreated cohorts can be found in the Supplement Table D3.2.

Table 3.2. Baseline Characteristics[17,18]

MLD Subtype		Late Infantile		Early Juvenile		
Arms		Presymptomatic Arsa-cel	Natural History	Presymptomatic Arsa-cel	Early Symptomatic Arsa-cel	Natural History
N		18	26	8	9	17
Follow-Up Median Years (Range)		6.1 (2.4 – 11.0)	4.4 (0.6 – 18.9)	3.3 (1.1 – 8.4)	7.2 (0.6 – 9.2)	5.6 (0.4 – 20.7)
Age at Diagnosis Median Months, (Range)		6.6 (0.4 – 12.3)	30.5 (18.6 – 44)	12.6 (0 – 44.1)	60.8 (24.9 – 131.7)	53.2 (30.9 – 91.3)
Age at Gene Therapy or First Contact Median Months, (Range)		10.3 (7.6 – 17.7)	18.8 (14.5 – 27.9)	16.1 (11.3 – 48.9)	66.7 (30.5 – 139.7)	52.6 (19.2 – 74.1)
Sex, n (%)	Male	13 (72)	12 (46)	6 (75)	6 (67)	9 (53)
Race, n (%)	White*	16 (89)	26 (100)	7 (88)	9 (100)	17 (100)
	Black	0	0	1 (13)	0	0
	Asian	2 (12)	0	0	0	0
GMFM-88 Total Score, at Baseline, Mean (SD)		47.2 (21.22)	NR	72.04 (18.11)	92.4 (6.69)	NR
ARSA Activity Level Median, nmol/mg/h		25.79†	NR	25.79†	25.79†	NR

ARSA: arylsulfatase A, GMFM: gross motor function measure, MLD: metachromatic leukodystrophy, N: total number, NR: not reported, SD: standard deviation, %: percent
*Including Caucasian, North African and Arabian Heritage
†Values were imputed because the actual values were below the lower limits of quantification or not detected or not quantifiable.

3.2. Results

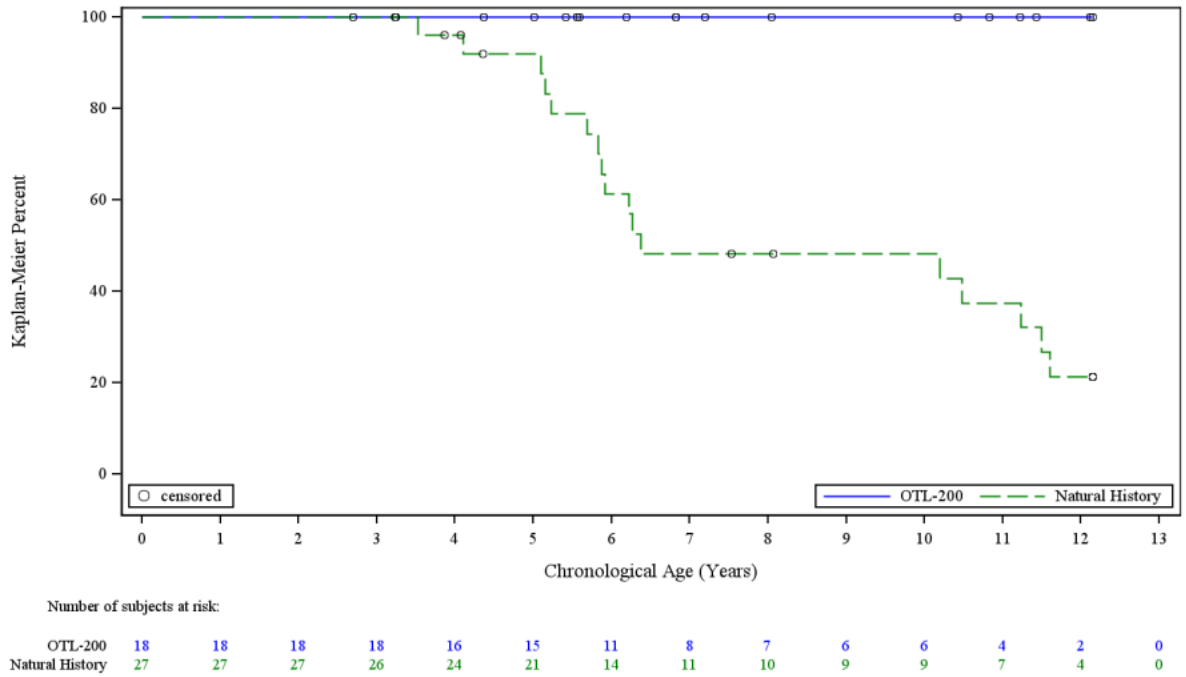
Because of the length of the enrollment period (over ten years), not all arsa-cel patients reached specific follow-up points. Additionally, all arsa-cel treated MLD patients were reported to have deviated from the protocol with a missed or out of window assessment. Thus, not every patient contributed to each outcome at every timepoint.

Clinical Benefits

Overall Survival

Data submitted by the manufacturer included unadjusted Kaplan-Meier curves for overall survival comparing all three treated subtypes of MLD with the LI and EJ-MLD untreated cohort. Since patients entered the study at different ages and different times, the survival curves are presented as chronological age (years). There were no deaths in up to 11 years of follow-up (up to 12 years of chronological age) in the presymptomatic LI-MLD group treated with arsa-cel. In the natural history cohort, the probability for survival at 12 chronological years was 0.23 (Figure 3.1).[17]

Figure 3.1. Kaplan-Meier Plot for Survival by Chronological Age for Late Infantile MLD Patients [17]



In contrast to the LI-MLD subtype, there was not as large a difference in survival probabilities across treated EJ-MLD patients and those in the natural history cohort. In the pre-symptomatic EJ-MLD group (n=8), there was one death 415 days after arsa-cel infusion that was deemed unrelated to gene therapy or MLD; the survival probability was 0.88 up to 11 years of chronological age (Figure 3.2). In the early symptomatic EJ-MLD groups treated with arsa-cel (n=9), there were no deaths up to 19 years of chronological age, based on data provided by the manufacturer (Figure 3.3).[17] Two deaths occurred in early symptomatic EJ-MLD patients due to disease progression;[6] however, as we noted earlier these two patients were excluded from analyses provided by the manufacturer because they would not have met current criteria for arsa-cel treatment and thus are not included in the data presented in Figure 3.3.

Figure 3.2. Kaplan-Meier Plot for Presymptomatic Early Juvenile MLD Patients [17]

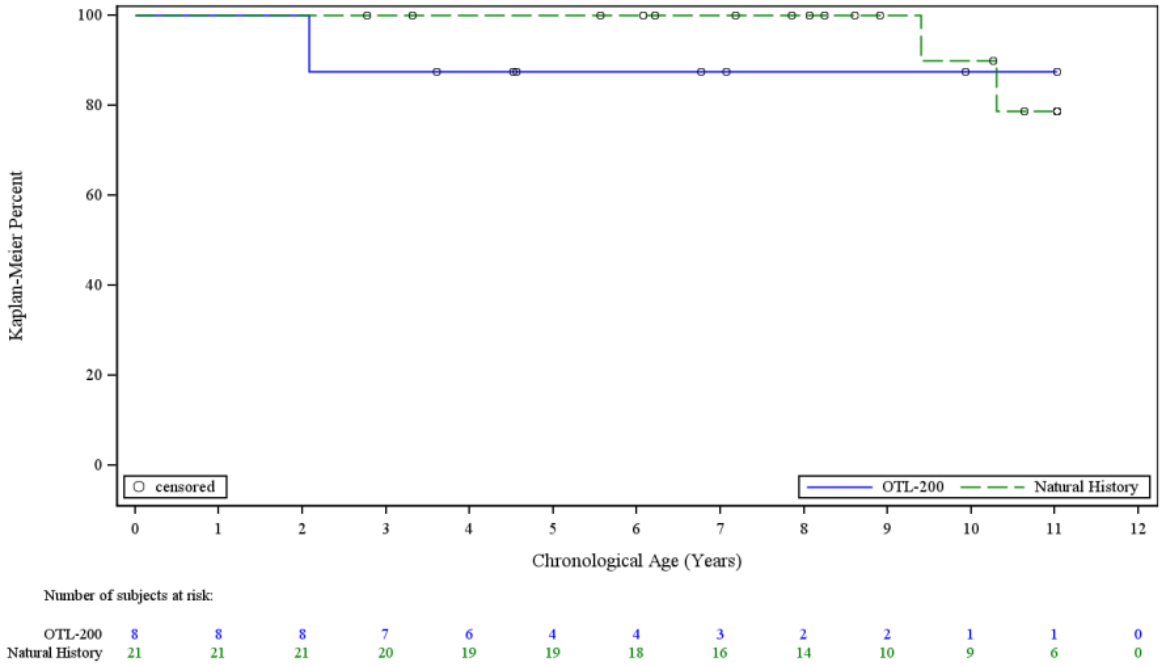
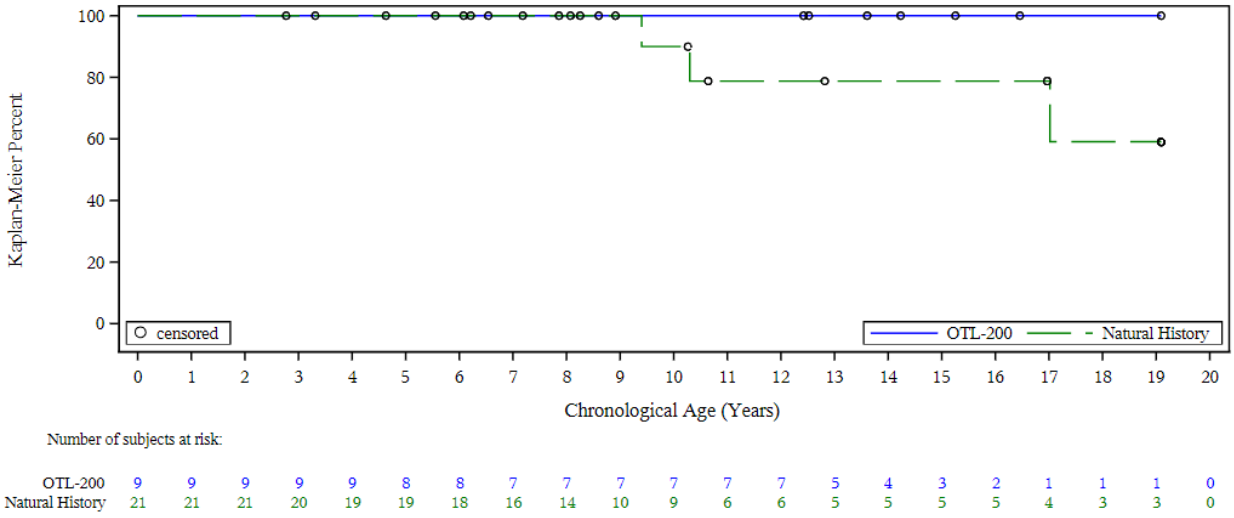


Figure 3.3. Kaplan-Meier Plot for Early Symptomatic Early Juvenile MLD Patients [17]



* Two additional early symptomatic EJ-MLD patients were excluded from analyses provided by the manufacturer, as these two patients would not have met current criteria to be treated with arsa-cel.

GMFM-88 score

Data submitted by the manufacturer suggested that GMFM-88 scores were measured in all treatment groups and then compared with the median total GMFM-88 for age-matched patients in the natural history cohort at years two and five only. At 24 months, all arsa-cel treated patients had

much higher GMFM-88 total scores compared to the natural history cohort (treatment difference of 76.75 for pre-symptomatic LI-MLD patients, 45.75 for pre-symptomatic EJ-MLD, and 48.89 for early symptomatic EJ-MLD patients). All MLD patients, regardless of their subtypes, also had substantially higher GMFM-88 scores compared to the natural history cohort patients at year five.[17] See Table 3.3.

Table 3.3. GMFM-88 Scores[17]

Arms	Late Infantile		PS Early Juvenile		ES Early Juvenile	
	Arsa-cel	Natural History	Arsa-cel	Natural History	Arsa-cel	Natural History
Year 2						
N Evaluated	16	11	7	8	9	13
GMFM Total Score, Median	81.55	4.80	92.71	46.96	88.47	39.58
Treatment Difference	76.75		45.75		48.89	
Year 5						
N Evaluated	7	9	2	8	3	7
GMFM Total Score, Median	87.92	1.51	100	8.09	48.36	2.29
Treatment Difference	86.41		91.91		46.07	

95% CI: 95 percent confidence interval, Arsa-cel: atidarsagene autotemcel, ES: early symptomatic, GMFM: Gross Motor Function Measure, N: total number, NR: not reported, PS: pre-symptomatic, %: percent

ARSA Activity Levels

ARSA activity levels increased in all groups to normal or supranormal levels after treatment with arsa-cel (See Table 3.4). The manufacturer provided long-term data on 35 MLD patients with up to 11 years of follow-up which suggested that none of the treated patients had PBMC ARSA activity level below the reference range during extended follow-up.[17]

Table 3.4. ARSA Activity in PBMCs in Arsa-cel Treated Patients

Trial	Phase I/II, Phase II, Expanded Access Programs[17]					
Timepoint	Pre-symptomatic Late Infantile (N=18)		Pre-symptomatic Early Juvenile (N=8)		Early Symptomatic Early Juvenile (N=9)	
	n	Median† (nmol/mg/h)	n	Median† (nmol/mg/h)	n	Median (nmol/mg/h)
Baseline	16	25.8*	8	25.8*	9	25.8*
Year 1	18	2028.5	8	771.6	9	169.4
Year 2	16	934.6	7	1242.3	8	88.4
Year 3	15	1557.1	4	1156.1	7	279.8
Year 4	1	1352.5	3	2217.9	4	703.9
Year 5	8	714.3	1	3234.1	3	362.9
Year 6	5	663.3	2	1311.5	2	1264.8
Year 7	6	963.4	1	1836.0	NR	NR
Year 8	4	114.4	1	779.8	NR	NR
Year 9	1	599.2	NR	NR	NR	NR
Year 10	1	328.0	NR	NR	NR	NR
Year 11	2	1357.5	NR	NR	NR	NR

*Values were imputed because the actual values were below the lower limits of quantification or not detected or not quantifiable.
†Data for single patients are not medians.

GMFC-MLD

GMFC-MLD was used to assess the motor function ranging from walking independently (level 0 or 1) to loss of all locomotion (level 6). Each of these levels is defined in Supplement Section A1. Overall, data provided by the manufacturer suggested that patients in the natural history cohort progressed to the next GMFC level more rapidly than those treated with arsa-cel.[17] While some patients with presymptomatic LI-MLD progressed to higher GMFC levels, all eight patients in the presymptomatic EJ-MLD group remained at GMFC 0 until last follow-up. See Table 3.5.

Table 3.5. Time from Predicted/Actual Disease Onset to GMFC-MLD Level

Trial	Phase I/II, Phase II, Expanded Access Programs[17]									
GMFC-MLD Level	Presymptomatic Late Infantile (N=18)		Late Infantile Natural History (N=26)		Presymptomatic Early Juvenile (N=8)		Early Symptomatic Early Juvenile (N=9)		Early Juvenile Natural History (N=17)	
	n	Median months*	n	Median months	n	Median months	n	Median months	n	Median months
Level 0	18	NC	0	-	8	NC	9	NC	0	0
Level 1	11	9.7	11	0.4	0	-	8	32.6	16	0.98
Level 2	4	2.3	19	6.2	0	-	6	44	13	13.5
Level 3	1	32.8	12	12.2	0	-	4	76.6	2	17.8
Level 4	1	44.8	11	13	0	-	3	75.4	5	28.6
Level 5	1	66.4	13	16.7	0	-	2	115.6	9	33.9
Level 6	1	98.8	26	19.3	0	-	0	-	11	40.2

GMFC-MLD: Gross Motor Function Classification for MLD, n: number, N: total number, NC: not calculable
*Data for single patients are not medians.

Cognitive Function

Patients treated with arsa-cel (n=35) were assessed for changes in cognitive performance via a Performance Standard Score (PSS) and Development Quotient Performance Score (DQp). Cognitive function was shown to be preserved in almost all treated patients, based on data provided by the manufacturer, compared to severe cognitive decline in patients in the natural history cohort. Except for one presymptomatic LI and one early symptomatic EJ-MLD patient, the arsa-cel treated patients who had PSS data continued to maintain stable scores up to 8-years of chronological age, indicating no decline in their cognitive function. However, beyond 8-years of chronological age, four arsa-cel treated LI-MLD patients had PSS scores below 85 at their last follow-up, indicating that the duration of benefit for cognitive function may vary. Of note, cognitive function did not decline in the majority of patients with EJ-MLD treated with arsa-cel even with some motor impairment (i.e., higher GMFC level) whereas it severely declined for those in the natural history cohort even at early stages of motor impairment.[17] See Supplement Figures D2.1-D2.3. and Supplement Table D3.12.

Additional Endpoints

Data from all published studies and presentations are provided in the supplement for both primary and secondary outcomes of these two trials. Overall, arsa-cel treated patients had also improvement in other measured outcomes. For example, treated LI-MLD patients had evidence of less degradation on nerve conduction velocity studies and less damage to the brain on MRI than the natural history cohort. None of the trials collected data on health-related quality of life (HRQoL). Details regarding these additional outcomes can be found in Supplement Section D2.

Harms

Adverse event severity was defined using the Common Terminology Criteria for Adverse Events (CTCAE). See Supplement Section A1 for CTCAE adverse event grade definitions.

Harms were categorized in relation to busulfan conditioning (pre-treatment phase), infusion of arsa-cel (treatment phase), acute phase immediately following infusion, and three months post gene therapy. In the pre-treatment phase, almost one-third of patients experienced a severe adverse event (grade 3 or higher), and an additional 13% of patients had a device-related infection. (Supplement Table D3.14). In the treatment phase, 26% of patients experienced a severe adverse event, with metabolic acidosis the most common reported adverse event. No severe adverse events, grade 3 or higher, were reported in the acute phase of the treatment. Almost all participants (95%, n=37) experienced a grade 3 adverse event during the three months after treatment, however the majority of these were related to conditioning regimen. In particular, three patients (8%) had a grade 4 adverse event. The most frequent grade 3 adverse events were febrile

neutropenia (82%), stomatitis (74%), and neutropenia (21%). Veno-occlusive disease was noted in 5% of patients.[17] See Supplement Table D3.14 for more detail.

One death was reported in the arsa-cel treated pre-symptomatic EJ-MLD group within the 35 patients analyzed by the manufacturer. The patient died of ischemic cerebral infarction 415 days after treatment. Two early symptomatic EJ-MLD patients experienced rapid disease progression and died at eight and 15 months after treatment after their families declined G-tube placement.

Subgroup Analyses and Heterogeneity

There were no subgroup analyses based on the 35 patients analyzed by the manufacturer. Exploratory subgroup analyses with matched siblings were done with an earlier data set; see Supplement for details. No other subgroup analysis based on sex, race, or ethnicity was evaluated because of limited trial sample size. We had no concerns about heterogeneity between the clinical trials and EAF and CUP patients, as eligibility criteria and protocols were similar regardless of where the child was treated.

Uncertainty and Controversies

The currently available data demonstrate that treatment with arsa-cel in presymptomatic LI and EJ-MLD and early symptomatic EJ-MLD preserves motor and cognitive function and extends survival compared with historical controls. However, the data are drawn from small, single-arm studies with comparison to a natural history cohort due to the difficulty and ethics of conducting randomized trials for ultra-rare diseases such as MLD. Such single-arm studies are subject to bias, 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 GMFM-88 scores were not necessarily collected at the same timepoints as in the trial – making direct comparisons difficult.

The long-term durability of arsa-cel is not known, particularly since patients would likely be treated in infancy or early childhood and follow-up in the current studies ranges from 2.4 – 11 years for LI-MLD patients and 0.6-9.2 years for EJ-MLD patients. That ARSA levels do not seem to have deteriorated over time in most patients is promising; however, what level of ARSA is adequate to prevent progression of disease is uncertain, since the correlation between ARSA levels and clinical outcomes such as GMFM-88 and GMFC is not known. 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 arsa-cel treatment. 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.

Short-term harms from arsa-cel treatment appear primarily to be due to the busulfan conditioning regimen in preparation for autologous stem-cell transplant, with all patients suffering with a grade 3 or higher adverse event at some time during the treatment course. Additionally, a few patients did have progression of MLD after treatment; it is unclear whether this is due to the busulfan or arsa-cel treatments themselves or if these patients were about to enter or were already in a progressive phase that would have occurred with or without treatment. Bone marrow conditioning itself can be expected to infrequently result in death in some children due to prolonged neutropenia in the peri-transplant period, although this risk is expected to be lower than with allogenic HSCT. While such deaths were not seen in the studies of arsa-cel, caregivers and clinicians will need to consider this risk.

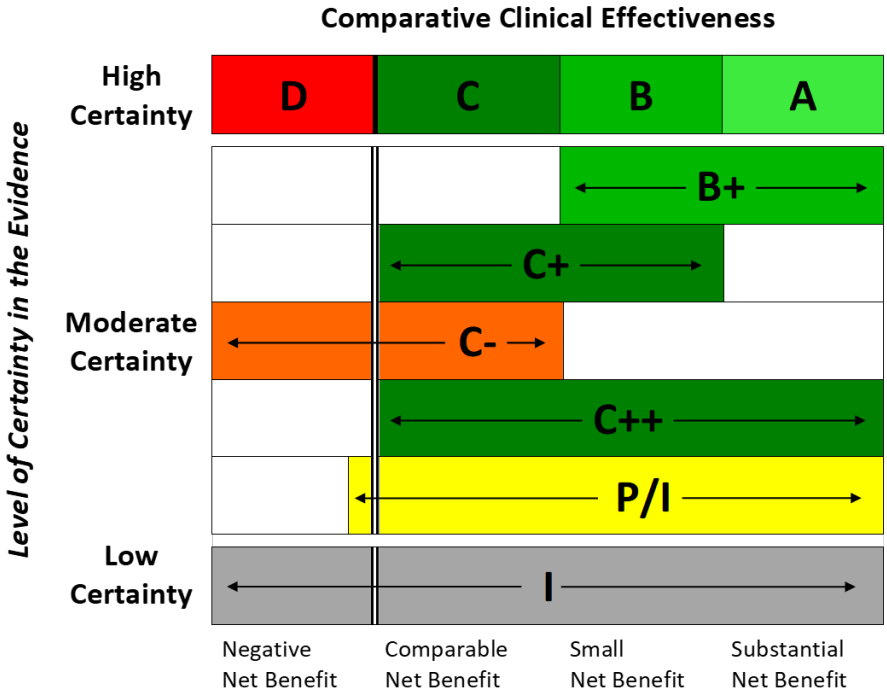
There were three deaths reported within the Phase I/II and Phase II studies. One death occurred in a patient with presymptomatic EJ-MLD; this death was thought not to be due to arsa-cel. Two of the deaths were in the early symptomatic EJ-MLD group; in these patients, death was thought to be due to disease progression after treatment. These two 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 two patients creates greater uncertainty about the potential harms in the early symptomatic EJ-MLD population. Finally, longer-term harms of arsa-cel are not yet known; however, 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.

Treatment with arsa-cel appears to be more effective in the presymptomatic phase, since existing neurological damage cannot be reversed with current therapies. Universal newborn screening has been advocated for as the best way to identify presymptomatic patients, since in children without a known MLD-affected sibling, it is very rare to be diagnosed before symptoms appear. However, although genotype-phenotype correlation with known mutations is high[20], particularly among siblings, there remains uncertainty about whether there may be previously unrecognized mutations that result in mild disease where the harms of arsa-cel may exceed benefit, particularly in the long-term. More and longer-term data on efficacy and harms are needed to understand whether these results could be applied to a newborn screening-detected disease population.

3.3. Summary and Comment

An explanation of the ICER Evidence Rating Matrix (Figure 3.4) is provided here.

Figure 3.4. ICER Evidence Rating Matrix



A = "Superior" - *High certainty of a substantial (moderate-large) net health benefit*
B = "Incremental" - *High certainty of a small net health benefit*
C = "Comparable"- *High certainty of a comparable net health benefit*
D= "Negative"- *High certainty of an inferior net health benefit*
B+= "Incremental or Better" – *Moderate certainty of a small or substantial net health benefit, with high certainty of at least a small net health benefit*
C+ = "Comparable or Incremental" - *Moderate certainty of a comparable or small net health benefit, with high certainty of at least a comparable net health benefit*
C- = "Comparable or Inferior" *– Moderate certainty that the net health benefit is either comparable or inferior with high certainty of at best a comparable net health benefit*
C++ = "Comparable or Better" - *Moderate certainty of a comparable, small, or substantial net health benefit, with high certainty of at least a comparable net health benefit*
P/I = "Promising but Inconclusive" *- Moderate certainty of a small or substantial net health benefit, small (but nonzero) likelihood of a negative net health benefit*
I = "Insufficient" – *Any situation in which the level of certainty in the evidence is low*

Without effective treatments, the early-onset forms of MLD are devastating and rapidly fatal. Thus, although therapy with arsa-cel has only been studied in 39 children in single arm studies so far, it appears to be an effective treatment with presymptomatic LI and presymptomatic or early symptomatic EJ-MLD, preventing onset or delaying progression of disease, as reflected in the preservation of motor and cognitive function and extension of survival in treated patients compared with usual care in the natural history cohort. The preservation of function resulting from arsa-cel treatment may drastically improve the quality of life of children with MLD and their

families, as normal or near-normal cognitive and motor function allows children to achieve milestones (e.g., attendance at school) that are otherwise lost due to the severity of untreated disease.

There are remaining questions about the durability and long-term harms of arsa-cel, particularly given that the treatment is likely to be given to young children. This is a particular issue in the early symptomatic EJ-MLD population, which did not appear to have as much benefit from treatment as the presymptomatic LI and EJ-MLD populations. Additionally, there were three deaths recorded during the trial; although based on the data available these were determined not to be related to treatment with arsa-cel, the sample size was small so the evidence is uncertain. As discussed above, bone marrow conditioning itself can be expected to result in some deaths.

Without treatment, children with **presymptomatic LI-MLD and presymptomatic EJ-MLD** will develop rapid physical and cognitive deterioration within a relatively short period of time. Treatment with arsa-cel dramatically alters this natural history and, at least for a number of years, appears to prevent deterioration in many, if not most, patients. There are harms from busulfan conditioning, including a risk of death, however these are clearly outweighed by the benefits of treatment. As such, for arsa-cel treatment 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 a normal health state, treatment with busulfan carries a risk of death, and long-term outcomes are less certain, since treatment with arsa-cel does not reverse pre-existing neurologic damage and it is possible that treatment may hasten progression of physical and cognitive decline prior to stabilization. Additionally, some treated patients do not achieve stability and so will have spent some remaining relatively healthy time dealing with the consequences of bone marrow conditioning with only partial benefit. Additionally, two patients with EJ-MLD had early deaths in the setting of disease progression; although entry criteria were changed post-hoc to exclude entry of similar patients, this creates additional uncertainties. Given these issues, for arsa-cel treatment 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+"**). Additionally, we heard from families for whom the risk of progression of symptoms during the treatment phase with arsa-cel (and before stabilization) is an important factor in the decision-making process, as a child may stabilize in a substantially worse state than their pre-treatment function. For these families, the level of certainty about the potential risk and extent of progression during treatment is low. As a result, the current data are insufficient to allow such families to make an informed decision about arsa-cel treatment for their child.

Table 3.6. Evidence Ratings

Treatment	Comparator	Evidence Rating
Presymptomatic LI MLD		
Arsa-cel	Usual care	A
Presymptomatic EJ MLD		
Arsa-cel	Usual care	A
Early Symptomatic EJ MLD		
Arsa-cel	Usual care	B+

CTAF Votes

Table 3.5. CTAF Votes on Comparative Clinical Effectiveness Questions

Question	Yes	No
Patient Population: *Children with presymptomatic late infantile MLD.* Is the currently available evidence adequate to demonstrate that the net health benefit of atidarsagene autotemcel (arsa-cel) is superior to that provided by usual care?	13	0
Patient Population: *Children with presymptomatic early juvenile MLD.* Is the currently available evidence adequate to demonstrate that the net health benefit of arsa-cel is superior to that provided by usual care?	13	0
Patient Population: *Children with early symptomatic early juvenile MLD.* Is the currently available evidence adequate to demonstrate that the net health benefit of arsa-cel is superior to that provided by usual care?	12	1

The panel unanimously voted that the evidence is adequate to demonstrate that the net health benefit of arsa-cel is superior to usual care for both the presymptomatic late infantile and presymptomatic early juvenile populations. The panel expressed some concern around population level screening accurately detecting presymptomatic children versus children who will not develop symptomatic MLD, however, ultimately decided a false-positive result from current diagnostics is not likely.

The great majority of the panel voted that the evidence is adequate to demonstrate that the net health benefit of arsa-cel is superior to usual care for early symptomatic early juvenile populations. The panel expressed concerns for the rapid progression of decline after initial symptoms, as well as poor level of functioning even after treatment. However, the panel focused on stopping the progression as soon as possible, even if there may be loss of functioning due to late diagnosis and treatments.

4. Long-Term Cost Effectiveness

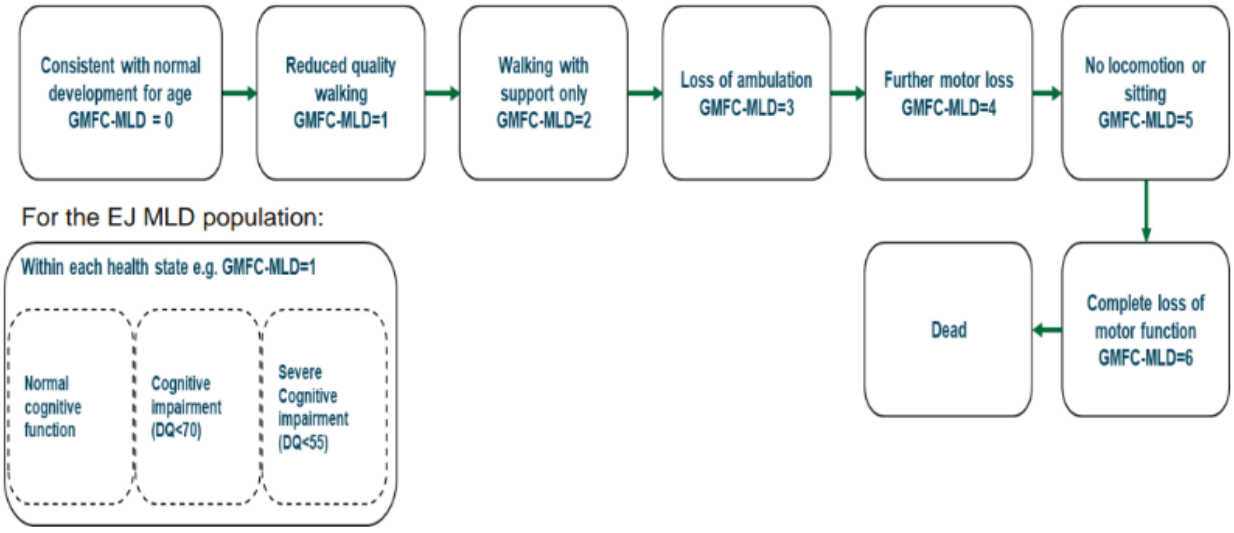
4.1. Methods Overview

We developed a *de novo* decision analytic model informed by key clinical trials and prior relevant economic models.[21-23] Costs and outcomes were discounted at 3% per year and a half-cycle correction was implemented. Our analysis reports results from a health care system perspective and a modified societal perspective (i.e., including caregiver productivity and quality of life impacts). The modified societal perspective was included as a co-base case given that caregiver productivity costs are high relative to direct health care costs, and the impact of arsa-cel treatment on these costs is substantial.

The model focused on an intention-to-treat analysis, with a hypothetical cohort of patients with MLD being treated with arsa-cel entering the model. Specifically, the model included patients with presymptomatic late infantile MLD (LI-MLD), presymptomatic early juvenile MLD (EJ-MLD), and early symptomatic EJ-MLD. Model cycle length was monthly, based on what was observed in prior published economic models and clinical data by the manufacturer.[21] The base case results are provided as a weighted average of outcomes for each subtype with weights based on the percent of patients in each subtype in the clinical trials (51% presymptomatic LI-MLD, 23% presymptomatic EJ-MLD, and 26% early symptomatic EJ-MLD).[6,18]

The Markov model structure was composed of eight health states, with seven health states determined by the Gross Motor Function Classification in MLD (GMFC-MLD) and death (Figure 4.1). The model consisted of sequential worsening health states. For each of the GMFC-MLD stage for EJ patients, three cognitive sub-states were also included to capture the combined effects of cognitive decline and motor function loss on patients. Transition probabilities varied by responder type (full responder, stable partial responder, and unstable partial responder) and were informed from clinical trial data and prior experience with gene therapy. [17,24,25] Similar to previously published models, it was assumed that patients could only die from their disease from GMFC-MLD state 6, but could die from other cause from any health state. Patients remained in the model until they died.

Figure 4.1. Model Structure



In response to public comments and internal model validation processes, changes to the economic evaluation between the draft Evidence Report and the revised Evidence Report included:

- Changing the stabilization period from 20 years to 12 years to align with clinical trial data.
    - After the stabilization period ends, patients are assumed to lose treatment durability at a probability of 0.02% per month at which point they transition to the unstable partial response group in the same GMFC-MLD health state.
- Revising the decline before the stabilization period begins for stable partial responders to align with clinical trial data.
- Using the utilities that include negative values in the base case and using the rescaled, non-negative utilities in a scenario analysis.
- Using caregiver disutilities that vary by disease severity in the co-base case modified societal perspective analysis, and using the consistent caregiver disutility in a scenario analysis.
- Using age-adjusted utilities for GMFC health state 0 in the late infantile and early juvenile subtypes.
- Using the lower value between age-adjusted utility or MLD-specific utility for GMFC health states 1 and 2 for patients with normal cognitive function.
- Conservative and optimistic scenario analyses for the stabilization period have been revised to 5 years and 50 years, respectively.

4.2. Key Model Assumptions and Inputs

Medical and non-medical costs, patient utility, and caregiver disutility depended on the patient's health state and was calculated for the entire modeled cohort on a monthly basis. Treatment effects in the model impacted costs and QALYs by extending time in specific GMFC-MLD health states, delaying time until death, and by having different adverse event (AE) profiles.

Our model included several assumptions stated below.

Table 4.1. Key Model Assumptions

Assumption	Rationale
Three categories of treatment response: full response, stable partial response, unstable partial response.	The manufacturer and previous HTA evaluations found evidence of heterogeneity in patients' response to the treatment based on clinical trial data. Patients categorized as full response initiated the period of stabilization immediately. Stable partial responders initiated the period of stabilization after an initial one year period of worsening. Unstable partial responders had a consistent trend of worsening but at a slower rate than the usual care cohort.
Stabilization periods for full and stable partial responders lasted 12 years followed by a probability (0.02% per month) of patients transitioning to the unstable partial responder group in the same GMFC health state for the remaining time horizon.	There is considerable uncertainty regarding the durability of effect of arsa-cel. The longest patient followed up to date is 12 years and treatment durability remained. Previous ICER reports for LentiGlobin gene therapies have assumed cellular turnover would be expected to occur over time at a 0.02% probability per month.[24,25]
Patients can only become progressively worse (i.e., move to a higher GMFC-MLD state).	The modeling approach assumed that patients cannot improve to a better health state. This approach simulated the MLD progression where patients do not improve once they progressed.
Patients only die from GMFC-MLD state 6	In the TIGET natural history study that served as the primary data source for our natural history progression estimates, death from MLD is preceded by loss of all motor function (GMFC-MLD 6). The approach was also validated with clinical experts in previous studies who confirmed that patients will progress through all GMFC-MLD states prior to death due to MLD.[22,23]
A proportion of patients were assumed to die in the first model cycle due to acute risk associated with transplant	The model included a 1.4% risk of death from infusion work for gene therapy in line with ICER's beta thalassemia report.[24]

EJ-MLD: early juvenile metachromatic leukodystrophy, FINOSE: Finland, Norway, and Sweden, GMFC-MLD: Gross Motor Function Classification in MLD, HTA: health technology assessment, MLD: metachromatic leukodystrophy, NICE: National Institute for Health and Care Excellence, TIGET: Telethon Institute for Gene Therapy

Interventions

The list of interventions was developed with input from patient organizations, clinicians, manufacturers, and payers on which treatments to include. The full list of interventions was as follows:

- atidarsagene autotemcel (OTL-200 or "arsa-cel", brand name Libmeldy™ in Europe)

Comparators

The comparator for this intervention was: usual care ("UC"; a multisystem care approach for physiotherapy and avoidance of contractures, spasticity, respiratory problems, nutrition-percutaneous endoscopic gastrostomy for swallowing difficulties, occupational therapy and speech and swallowing maintenance therapy, constipation, and pain).

Clinical Inputs

Clinical inputs were derived from data submitted by the manufacturer, published clinical trials, and prior economic analyses in MLD and other gene therapies. Inputs related to arsa-cel such as administration, monitoring, and adverse events are detailed in the Supplement.

Transition Probabilities

In each cycle, patients could either stay in the same health state, transition into the next GMFC-MLD health state, or transition to death. Individuals could only progress to the next GMFC-MLD state (e.g., from GMFC-MLD 1 to GMFC-MLD 2) and could not improve (patients could not transition from GMFC-MLD 1 to GMFC-MLD 0).

Transition probabilities for the usual care arm were estimated from natural history data on mean time in each successive GMFC-MLD level using an exponential distribution. (Supplement Table E2.1).[22] Transition probabilities for the arsa-cel arms were derived as follows: 1) Full responders experienced stabilization for 12 years (i.e. no disease progression) after which they reverted to the unstable partial responder group in the same GMFC-MLD health state at a rate used in ICER's beta thalassemia and sickle cell disease reports that assessed gene therapies (0.271% annually or 0.02% monthly) for the remainder of the model lifetime time horizon; [24,25] 2) Stable partial responders experienced transitions for the first year using modified monthly transition probabilities based on manufacturer submitted data (Supplement Table E2.2) that aligned with clinical trial data results. This was followed by a stabilization period for 12 years, followed by the same reversion transition probabilities mentioned above for the full responders where they transition to the unstable partial responder groups; and 3) Unstable partial responders experienced delayed progression versus natural history, implemented using progression multipliers derived as the ratio of the mean time

spent in each GMFC-MLD health state for arsa-cel versus natural history. The modifiers used were based on manufacturer submitted data (Supplement Table E2.2).

Discontinuation

Since arsa-cel is administered as a one-time infusion, there were no discontinuations in the model.

Mortality

Disease specific survival was based on natural history data on mean time in the GMFC 6 health state. Background mortality was included for all health states. For arsa-cel, overall survival was extended in relation to the stabilization period (full and stable partial responders) and delayed progression (unstable partial responders).

Heterogeneity and Subgroups

Prior HTA submissions to FINOSE and NICE included the use of subgroups based on categories of response as detailed below to inform the cost-effectiveness model.[22,23] Three categories of treatment response were used: full response, stable partial response, and unstable partial response. The description of each and the distributions used are in Table 4.2.

Table 4.2. Treatment Response Subtype and Associated Proportions

Treatment Response	Description	Proportion[22,23]
Full Response	Motor and cognitive function remain stable (e.g., 12 years) followed by a 0.02% monthly probability of transitioning to the unstable partial responder group in the same GMFC-MLD health state	33% presymptomatic LI-MLD 100% presymptomatic EJ-MLD 0% early symptomatic EJ-MLD
Stable Partial Response	Motor and cognitive function remain stable (e.g., 12 years) after an initial period of worsening (1 year), followed by a 0.02% monthly probability of transitioning to the unstable partial responder group in the same GMFC-MLD health state	61% presymptomatic LI-MLD 0% presymptomatic EJ-MLD 44% early symptomatic EJ-MLD
Unstable Partial Response	A consistent trend of worsening in motor and/or cognitive function, but at a slower rate than natural history	6% presymptomatic LI-MLD 0% presymptomatic EJ-MLD 56% early symptomatic EJ-MLD

Health State Utilities

Health state utilities were derived from publicly available literature and/or manufacturer submitted data and applied to health states. We used utilities that were elicited for LI and EJ-MLD from the United Kingdom (UK).[14] Health state descriptions for GMFC-MLD states in MLD were developed using a literature review and qualitative clinician interviews (n=6), who had experience in treating

patients with MLD (n=5) and assessing the cognitive performance of patients with MLD (n=1). These health states were then valued by the UK general public using the time trade off method. Participants evaluated the LI-MLD health states (n=100) and different participants evaluated the EJ-MLD health states (n=101). The utility values were then adjusted to reflect the preferences of the US general population (Table 4.3).[26]. For GMFC-MLD state 0 for late infantile and normal cognitive function in early juvenile, we used age-adjusted general population estimates.[27]. Additionally, we used the lower value between the age-adjusted general population estimates and the MLD-specific estimate from Table 4.3 for GMFC-MLD states 1 and 2 for normal cognitive function as utility is expected to decrease with age instead of staying constant. Many utilities in the more progressed GMFC-MLD states had negative values, which pose challenges and limitations that have been discussed elsewhere.[22] As a result, we performed a scenario using a rescaled utility set that did not allow for negative values detailed in the supplement.

Table 4.3. Health State Utilities

Health State	Late Infantile	Early Juvenile		
		Normal Cognitive Function	Moderate Cognitive Impairment	Severe Cognitive Impairment
GMFC 0	Age adjusted general population		0.75	0.46
GMFC 1	0.71	0.91	0.63	0.34
GMFC 2	0.44	0.84	0.56	0.27
GMFC 3	-0.04	0.38	0.10	-0.11
GMFC 4	-0.13	0.00	-0.16	-0.33
GMFC 5	-0.20	-0.08	-0.25	-0.41
GMFC 6	-0.27	-0.13	-0.29	-0.46

GMFC-MLD: Gross Motor Function Classification in MLD

Caregiver disutilities were applied in the co-base case modified societal perspective. Prior research has shown that caregivers of children with LI-MLD and EJ-MLD have significantly lower quality of life (QoL) scores than parents of children without chronic conditions.[28] Disutility was estimated in a study of caregivers of MLD patients but the data were collected in a way that did not account for disease severity, which intuitively lacked face validity.[29] As a result, these disutilities were used as a scenario analysis (Supplement Table E2.6). Instead, in the base case, caregiver disutilities were informed by another enzyme replacement therapy for the treatment of another rare progressive neurodegenerative disease, neuronal ceroid lipofuscinosis type 2 (CLN-2). The caregiver disutilities for CLN-2 were obtained in the ICON study, which reported on the challenges of living with and caring for children affected with CLN-2.[30] The GMFC-MLD health states were then aligned to CLN-2 states based on motor and language disease characteristics.[31] For GMFC-MLD 3, the average utility for CLN-2 states 4 and 5 were assumed. The resultant caregiver disutilities that were aligned between CLN-2 and MLD are shown in Table 4.4.

Table 4.4. Caregiver Disutility by GMFC-MLD Stage from CLN-2 Health States

CLN-2 Health State	Disutility	GMFC-MLD Stage	Total Caregiver Disutility
1	-0.02	0	0
2	-0.025	1	-0.02
3	-0.027	2	-0.027
4	-0.054	3	-0.0675
5	-0.081	4	-0.108
6	-0.108	5	-0.135
7	-0.135	6	-0.189
8	-0.162		
9	-0.189		

GMFC-MLD: Gross Motor Function Classification in MLD; CLN-2: neuronal ceroid lipofuscinosis type 2

Cost Inputs

All costs used in the model were updated to 2023 dollars.

Drug Costs

For arsa-cel, we estimated the placeholder price based on prior submitted health technology assessment documents in other countries. Specifically, we used the price of Norwegian Krone (NOK) 30,074,576, which converted to $2,800,240 using the purchasing price parity for Norway (Table 4.5).[22]

Table 4.5. Drug Costs

Drug	WAC per Dose
atidarsagene autotemcel (Libmeldy™)	$2,800,240*

WAC: wholesale acquisition cost

*placeholder price

Non-Drug Costs

Given that arsa-cel is an autologous *ex-vivo* genetically modified autologous $CD34^+$ HSPC gene therapy that is administered by IV infusion, there are administrative procedures and resultant costs associated with treatment. These are detailed in Supplement Table E2.4.

Costs to treat MLD were informed by a published study that assessed average cost by GMFC-MLD across nine European countries.[32] A bottom-up approach was used to determine total healthcare resource utilization based on six clinical experts in the UK. They provided quantified specific resource utilization data including frequency and proportion for MLD patients by GMFC-MLD stage. These estimates were then corroborated by clinical experts in other European countries. The clinical experts determined that management of MLD in Europe would not differ significantly to the

US, so US-specific unit costs were applied to the healthcare resource utilization to estimate US costs (Table 4.6).

Table 4.6. Monthly Costs by GMFC-MLD Health State

Category	GMFC-MLD Health State						
	0	1	2	3	4	5	6
Drugs	$0	$121	$123	$123	$127	$150	$167
Medical Tests	$0	$202	$131	$131	$131	$132	$130
Medical Visits	$296	$169	$164	$289	$320	$282	$284
Hospitalizations	$0	$474	$1,422	$2,134	$3,360	$3,912	$14,236
PCP & Emergency	$0	$7	$10	$11	$15	$17	$20
Healthcare Equipment	$0	$43	$63	$3,484	$3,482	$3,489	$3,489
Respite Care	$0	$0	$0	$0	$0	$0	$0
Social Services	$0	$0	$0	$0	$0	$0	$1,732
Total	**$296**	**$1,015**	**$1,912**	**$6,171**	**$7,435**	**$7,981**	**$20,058**

GMFC-MLD: Gross Motor Function Classification in MLD, PCP: Primary care physician

Productivity Losses for Caregivers

Productivity losses for caregivers of patients with MLD were estimated from the International Caregiver Survey using the human capital approach.[29] While 21 caregivers from the UK, Germany, and the US participated in the study, productivity losses were informed from only US respondents (n=10). Using an annual average salary of $55,029, productivity losses were calculated as shown in Table 4.7. Since none of the US caregivers had patients in GMFC-MLD 5 or 6, the ratio of lost income from the UK and Germany (GMFC-MLD 5/6 : GMFC-MLD 3/4) was applied to US caregivers with patients in GMFC-MLD 3 or 4.

Table 4.7. Monthly Loss of Income for Caregivers of MLD Patients

MLD Disease Stage	GMFC-MLD Level	Mean Monthly Loss of Income
Mild	GMFC-MLD 1 and 2	$83
Moderate	GMFC-MLD 3 and 4	$2,405
Severe	GMFC-MLD 5 and 6	$4,019

GMFC-MLD: Gross Motor Function Classification in MLD

Out of pocket costs were also calculated from the International Caregiver Survey (Table 4.8). The same methodology was used as in productivity losses to inform out of pocket costs in GMFC-MLD 5 or 6.

Table 4.8. Monthly Out of Pocket Costs

MLD Disease Stage	GMFC-MLD Level	Mean Monthly Out of Pocket Costs
Mild	GMFC-MLD 1 and 2	$13
Moderate	GMFC-MLD 3 and 4	$503
Severe	GMFC-MLD 5 and 6	$121

GMFC-MLD: Gross Motor Function Classification in MLD

4.3. Results

Base-Case Results

The total discounted costs, quality-adjusted life years (QALYs) gained, equal-value life years (evLYs) gained, and life years (LYs) gained are detailed in Table 4.9 for arsa-cel compared to usual care. Base-case results are a weighted average of outcomes for each subtype (51% presymptomatic LI-MLD, 23% presymptomatic EJ-MLD, and 26% early symptomatic EJ-MLD). Over a lifetime horizon at the placeholder price of $2,800,000, treatment with arsa-cel resulted in higher incremental costs of approximately $2,389,000 and incremental gains in QALYs and evLYs of approximately 18.83 and 21.45, respectively, compared to usual care from the health care sector perspective. From the modified societal perspective at the placeholder price, treatment with arsa-cel resulted in high incremental costs of approximately $2,225,000 and incremental gains in QALYs and evLYs of approximately 19.26 and 22.43, respectively, compared to usual care over a lifetime horizon. The negative QALYs and evLYs for the usual care arm from both the health care sector and societal perspectives reflect the extreme severity of the disease and are due to the relatively longer time patients spend in states with negative utilities. The resultant incremental cost-effectiveness ratios are presented in Table 4.10.

Table 4.9. Results for the Base-Case for Arsa-cel Compared to Usual Care

Treatment	Drug Cost*	Total Cost	QALYs	evLYs	Life Years
Health care sector perspective					
Arsa-cel	$2,800,000*	$3,493,000	18.32	20.94	25.66
Usual care	$0	$1,104,000	-0.51	-0.51	7.44
Modified societal perspective					
Arsa-cel	$2,800,000*	$3,607,000	17.78	20.94	25.66
Usual care	$0	$1,383,000	-1.49	-1.49	7.44

evLY: equal-value of life-year, QALY: quality-adjusted life-year

*Based on placeholder price

Table 4.10. Incremental Cost-Effectiveness Ratios for the Base Case

Treatment	Comparator	Cost per QALY Gained*	Cost per evLY Gained*	Cost per Life Year Gained*
Health Care Sector Perspective				
Arsa-cel	Usual care	$127,000	$111,000	$131,000
Modified Societal Perspective				
Arsa-cel	Usual care	$115,000	$99,000	$122,000

evLY: equal-value of life-year, QALY: quality-adjusted life-year

*Based on placeholder price

Results by MLD subtype (presymptomatic LI-MLD, presymptomatic EJ-MLD, and early symptomatic EJ-MLD) are detailed in Table 4.11 to Table 4.16. From a cost per QALY gained and cost per evLY gained standpoint, arsa-cel resulted in more favorable ratios for the presymptomatic subtypes, especially for EJ-MLD.

Table 4.11. Results for the Presymptomatic LI-MLD subtype for Arsa-cel Compared to Usual Care

Treatment	Drug Cost*	Total Cost	QALYs	evLYs	Life Years
Health Care Sector Perspective					
Arsa-cel	$2,800,000*	$3,406,000	18.87	22.54	27.56
Usual care	$0	$1,081,000	-0.64	-0.64	6.20
Modified Societal Perspective					
Arsa-cel	$2,800,000*	$3,464,000	18.37	22.54	27.56
Usual care	$0	$1,336,000	-1.56	-1.56	6.20

evLY: equal-value of life-year, QALY: quality-adjusted life-year

*based on placeholder price

Table 4.12. Incremental Cost-Effectiveness Ratios for the Presymptomatic LI-MLD subtype

Treatment	Comparator	Cost per QALY Gained*	Cost per evLY Gained*	Cost per Life Year Gained*
Health Care Sector Perspective				
Arsa-cel	Usual care	$119,000	$100,000	$109,000
Modified Societal Perspective				
Arsa-cel	Usual care	$107,000	$88,000	$100,000

evLY: equal-value of life-year, QALY: quality-adjusted life-year

*based on placeholder price

Table 4.13. Results for the Presymptomatic EJ-MLD subtype for Arsa-cel Compared to Usual Care

Treatment	Drug Cost*	Total Cost	QALYs	evLYs	Life Years
Health Care Sector Perspective					
Arsa-cel	$2,800,000*	$3,122,000	25.16	24.90	28.56
Usual care	$0	$1,125,000	-0.24	-0.24	8.85
Modified Societal Perspective					
Arsa-cel	$2,800,000*	$3,138,000	25.11	24.90	28.56
Usual care	$0	$1,426,000	-1.28	-1.28	8.85

evLY: equal-value of life-year, QALY: quality-adjusted life-year

*based on placeholder price

Table 4.14. Incremental Cost-Effectiveness Ratios for the Presymptomatic EJ-MLD subtype

Treatment	Comparator	Cost per QALY Gained*	Cost per evLY Gained*	Cost per Life Year Gained*
Health Care Sector Perspective				
Arsa-cel	Usual care	$79,000	$79,000	$101,000
Modified Societal Perspective				
Arsa-cel	Usual care	$65,000	$65,000	$87,000

evLY: equal-value of life-year, QALY: quality-adjusted life-year

*based on placeholder price

Table 4.15. Results for the Early Symptomatic EJ-MLD subtype for Arsa-cel Compared to Usual Care

Treatment	Drug Cost*	Total Cost	QALYs	evLYs	Life Years
Health Care Sector Perspective					
Arsa-cel	$2,800,000*	$3,993,000	11.18	14.31	19.37
Usual care	$0	$1,132,000	-0.49	-0.49	8.64
Modified Societal Perspective					
Arsa-cel	$2,800,000*	$4,303,000	10.13	14.31	19.37
Usual care	$0	$1,436,000	-1.54	-1.54	8.64

evLY: equal-value of life-year, QALY: quality-adjusted life-year

*based on placeholder price

Table 4.16. Incremental Cost-Effectiveness Ratios for the Early Symptomatic EJ-MLD subtype

Treatment	Comparator	Cost per QALY Gained*	Cost per evLY Gained*	Cost per Life Year Gained*
Health Care Sector Perspective				
Arsa-cel	Usual care	$245,000	$193,000	$267,000
Modified Societal Perspective				
Arsa-cel	Usual care	$246,000	$181,000	$267,000

evLY: equal-value of life-year, QALY: quality-adjusted life-year

*based on placeholder price

We also assessed the time until loss of ambulation (GMFC-MLD state 3) for the base case and by subtype (Table 4.17). In the base case, patients treated with arsa-cel were projected to have loss of

ambulation after 23.14 years compared to 1.68 years for patients treated with usual care. Patients with the presymptomatic EJ-MLD subtype were projected to have the longest delay until loss of ambulation.

Table 4.17. Time (Years) Until Loss of Ambulation

	Arsa-cel	Usual care
Base Case	23.14	1.68
Presymptomatic Late Infantile	26.63	0.91
Presymptomatic Early Juvenile	27.99	2.61
Early Symptomatic Early Juvenile	12.00	2.36

Sensitivity Analyses

Results from one-way sensitivity analysis and probabilistic sensitivity analysis for arsa-cel can be found in Supplement Section E4.

Scenario Analyses

We conducted several scenario analyses to examine uncertainty and potential variation in the findings. The scenarios are detailed below and the results are presented in Tables E5.1 and E5.2.

1. Undiscounted costs and outcomes.
2. An optimistic and conservative assumption regarding the benefit of treatment. For arsa-cel, this translated to a stabilization period of 50 years and 5 years for the optimistic and conservative scenarios, respectively.
3. Rescaled utility estimates that did not allow for negative utility values.
4. 50/50 shared savings in which 50% of lifetime health care cost offsets from a new treatment are assigned to the health care system instead of being assigned entirely to the new treatment.
5. A consistent caregiver disutility regardless of disease severity.
6. Threshold analyses to calculate the price needed to meet commonly accepted cost-effectiveness thresholds for QALYs gained and evLY gained using the rescaled non-negative utility values.

Threshold Analyses

Threshold analyses were conducted to calculate the price needed to meet commonly accepted cost-effectiveness thresholds for QALY gained (Table 4.17) and evLY gained (Table 4.18). Additionally, threshold analyses were run using the rescaled non-negative utility values as a scenario analysis (Supplement Tables E5.3 and 5.4)

Table 4.18. QALY-Based Threshold Analysis Results

	Unit Price to Achieve $50,000 per QALY Gained	Unit Price to Achieve $100,000 per QALY Gained	Unit Price to Achieve $150,000 per QALY Gained	Unit Price to Achieve $200,000 per QALY Gained
Health Care Sector Perspective				
Arsa-cel	$1,353,000	$2,294,000	$3,236,000	$4,177,000
Modified Societal Perspective				
Arsa-cel	$1,539,000	$2,502,000	$3,465,000	$4,428,000

QALY: quality-adjusted life-year

Table 4.19. evLY-Based Threshold Analysis Results

	Unit Price to Achieve $50,000 per evLY Gained	Unit Price to Achieve $100,000 per evLY Gained	Unit Price to Achieve $150,000 per evLY Gained	Unit Price to Achieve $200,000 per evLY Gained
Health Care Sector Perspective				
Arsa-cel	$1,484,000	$2,557,000	$3,629,000	$4,702,000
Modified Societal Perspective				
Arsa-cel	$1,697,000	$2,818,000	$3,940,000	$5,061,000

evLY: equal-value life-year

Uncertainty and Controversies

The population of focus for the assessment is patients with presymptomatic LI-MLD, presymptomatic EJ-MLD, and early symptomatic MLD who are treated with arsa-cel. In our base case, we weighted the three subtypes by their estimated prevalence to produce a single incremental cost-effectiveness ratio. However, in the scoping phase of this assessment, we heard from several clinicians that these subtypes may be systematically different, and as such we provided subtype-specific results.

The model estimates for arsa-cel were driven by treatment response type and stabilization period. As previously mentioned, our model assumed there were three treatment responses: full response, stable partial response, and unstable partial response. Given the heterogeneity of the disease as well as the treatment effect heterogeneity seen in clinical trial results, including a small number of

patients who improved, it is possible that the number and definition of treatment response we used in the model are inadequate. Additionally, we used a stabilization period of 12 years for the full response and stable partial response. After this stabilization period, we assumed patients had a 0.02% monthly probability of transitioning to the unstable partial response within the same GMFC-MLD health state. This assumption was based on prior ICER assessments in gene therapy; in those assessments, the assumption was based on clinical expert opinion. It is possible that while valid for other gene therapies in other diseases, the probability of reversion to a less favorable treatment response category needs to be altered for arsa-cel in MLD. More mature clinical trial data will inform this assumption with time.

4.4 Summary and Comment

In our lifetime model, treatment of patients with presymptomatic LI-MLD, presymptomatic EJ-MLD, and early symptomatic EJ-MLD with arsa-cel resulted in gains in QALYs, evLYs, and life years compared to usual care. Using the current placeholder price, and after discounting future costs and outcomes at 3% per year, arsa-cel had an incremental cost-effectiveness ratio of $127,000 per QALY gained and $111,000 per evLYG from the health care sector perspective. The modified societal perspective produced similar results. While these ratios vary by subtype of MLD, we expect that arsa-cel will have a single price across treatment of patients with early forms of MLD, and so a blended analysis of this sort is most appropriate.

5. Contextual Considerations and Potential Other Benefits

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 was not available in the evidence base nor could be adequately estimated within the cost-effectiveness model. These elements are listed in the table below, with related information gathered from patients and other stakeholders. Following the public deliberation on this report the appraisal committee will vote on the degree to which each of these factors should affect overall judgments of long-term value for money of the intervention(s) in this review.

Table 5.1. Contextual Considerations

Contextual Consideration	Relevant Information
Acuity of need for treatment of individual patients based on short-term risk of death or progression to permanent disability	There are currently no effective disease-modifying treatments for children with early onset MLD (late infantile and early juvenile). Such children progress to disability and death during childhood without treatment.
Magnitude of the lifetime impact on individual patients of the condition being treated	Since children with LI and EJ-MLD typically die during childhood, an effective disease-modifying therapy would have a dramatic lifetime impact on individual patients.

Table 5.2. Potential Other Benefits or Disadvantages

Potential Other Benefit or Disadvantage	Relevant Information
Patients' ability to achieve major life goals related to education, work, or family life	Children with LI and EJ-MLD typically lose motor and cognitive functions over the course of the disease. Prevention of onset of motor and cognitive decline would have a dramatic impact on a child's ability to achieve major life goals.
Caregivers' quality of life and/or ability to achieve major life goals related to education, work, or family life	The caregiving impact of MLD is extremely high, as children who progress to severe disease require a substantial amount of caregiving, often causing a parent to leave the workforce, physical and mental distress, and cause significant disruption to family life. An effective disease-modifying therapy may substantially decrease the impact of the disease to caregivers and families.
Patients' ability to manage and sustain treatment given the complexity of regimen	Arsa-cel is a one-time gene therapy. If successful in preventing onset and progression of MLD, there may be reduced complexity in supportive care treatments as well as navigating insurance barriers to care.
Society's goal of reducing health inequities	MLD is more common in populations such as the western US Navajos and Alaska Natives, both of whom are underserved populations. Use of arsa-cel could reduce health inequities in these populations. Arsa-cel is likely to be expensive and offered only at specialized centers due to the rarity of the disease and the intensity of treatment. Poor insurance coverage of the treatment could worsen health inequities. Limitations in access to arsa-cel due to distance from a treatment center or limited finances could also worsen health inequities. Some patients with MLD are offered treatment with HSCT. However, patients from some minority populations are less likely to find unrelated donor matches and thus are less likely to be able to access HSCT. Because arsa-cel uses a patient's own cells for therapy, increased access to arsa-cel may reduce health inequities. ICER did not calculate the Health Improvement Distribution Index (HIDI) because of uncertainties in the prevalence estimates for MLD.
Other	An effective treatment for MLD may change the entire "infrastructure" of care, including effects on screening for affected patients, on the awareness of clinicians, and on the dissemination of understanding about the condition, that may revolutionize how patients are cared for in many ways that extend beyond the treatment itself.

CTAF VOTES

At the public meeting, the CTAF deliberated and voted on the relevance of specific potential other benefits and contextual considerations on judgments of value for the interventions under review. The results of the voting are shown below. Further details on the intent of these votes to help provide a comprehensive view on long-term value for money are provided in the ICER Value Assessment Framework.

When making judgments of overall long-term value for money, what is the relative priority that should be given to *any* effective treatment for metachromatic leukodystrophy, on the basis of the following contextual considerations:

Patient Population: *Children with presymptomatic late infantile MLD or presymptomatic early juvenile MLD*

Table 5.3. CTAF Votes on Contextual Considerations Questions

Contextual Consideration	Very Low Priority	Low priority	Average priority	High priority	Very high priority
Acuity of need for treatment of individual patients based on short-term risk of death or progression to permanent disability	0	0	0	1	12
Magnitude of the lifetime impact on individual patients of the condition being treated	0	0	0	0	13

Taking into account the severity of the disease, a majority of the CTAF panel assigned very high priority to any effective treatment for MLD when considering the acuity of need for treatment of individual patients based on short-term risk of death or progression to disability. Considering that MLD is a rapidly progressive and fatal condition, the entire panel agreed that given the magnitude of the lifetime impact on individual patients, very high priority should be given to any treatment.

What are the relative effects of arsa-cel versus usual care on the following outcomes that inform judgment of the overall long-term value for money of arsa-cel?

Patient Population: *Children with presymptomatic late infantile MLD or presymptomatic early juvenile MLD*

5.4. CTAF Votes on Potential Other Benefits or Disadvantages Questions

Potential Other Benefit or Disadvantage	Major Negative Effect	Minor Negative Effect	No Difference	Minor Positive Effect	Major Positive Effect
Patients' ability to achieve major life goals related to education, work, or family life	0	0	0	0	13
Caregivers' quality of life and/or ability to achieve major life goals related to education, work, or family life	0	0	0	0	13
Society's goal of reducing health inequities	0	0	7	6	0
Other: The entire "infrastructure" of care, including effects on screening for affected patients, on the awareness of clinicians, and on the dissemination of understanding about the condition, that may revolutionize how patients are cared for in many ways that extend beyond the treatment itself.	0	0	4	2	7

The CTAF panel unanimously voted that arsa-cel would have a major positive effect on both patients' and caregivers' ability to achieve major life goals related to education, work, or family life. The panel heard from patient experts that children with MLD go on to live 'normal lives' after receiving arsa-cel, in comparison to their affected siblings who did not receive the intervention. Patient representatives also shared how devastating the disease is for caregivers, quoting one parent, "This treatment doesn't just save a child, it saves a family."

About half of the panel agreed on arsa-cel having no effect on society's goal of reducing health inequities. Six voting members believed in a minor positive effect, considering some racial and ethnic disparities in MLD incidence. Patient and clinical experts reminded the CTAF panel of MLD's greater incidence in Native/Indigenous populations in the U.S, as well as in communities where consanguineous marriages are more frequent.

There were seven votes for arsa-cel's major positive effect on the entire "infrastructure" of care, including effects on screening, awareness of clinicians, and dissemination of understanding about MLD. Four panel members voted for no effect on the infrastructure of care, while two voted for a minor positive effect.

6. Health Benefit Price Benchmarks

Health Benefit Price Benchmarks (HBPBs) for the cost of treatment with arsa-cel are presented in Table 6.1 below. The HBPB for a drug is defined as the price range that would achieve incremental cost-effectiveness ratios between $100,000 and $150,000 per QALY or per evLY gained. For this assessment, the health care system perspective and the modified societal perspective were considered part of a co-base case. Therefore, both perspectives are included. The HBPB for arsa-cel ranges from $2,294,000 to $3,940,000.

Table 6.1. Cost-Effectiveness Threshold Prices for Arsa-cel

	Placeholder Price*	Price at $100,000 Threshold	Price at $150,000 Threshold
Health Care Sector Perspective			
QALYs Gained	$2,800,000	$2,294,000	$3,236,000
evLYs Gained	$2,800,000	$2,557,000	$3,629,000
Modified Societal Perspective			
QALYs Gained	$2,800,000	$2,502,000	$3,465,000
evLYs Gained	$2,800,000	$2,818,000	$3,940,000

evLY: equal value life year, QALY: quality-adjusted life year

*assumption

CTAF Votes

Long-term value for money votes were not taken at the public meeting because a net price for arsa-cel was not available.

7. Potential Budget Impact

7.1. Overview of Key Assumptions

Results from the cost-effectiveness model were used to estimate the potential total budgetary impact of arsa-cel for patients with MLD. We used a placeholder price of $2,800,240 per treated patient to be paid up front, the same as in the base case cost-effectiveness analysis, and the three threshold prices (at $50,000, $100,000, and $150,000 per QALY) for arsa-cel in our estimates of budget impact.

This potential budget impact analysis will include the estimated number of individuals in the US who would be eligible for treatment. There is considerable uncertainty in the prevalence and incidence of MLD in the US, and it is expected to vary among subpopulations. To estimate the size of the potential candidate populations for treatment, we used inputs for the number of live births in the US per year (2021 estimate of 3,659,289)[33] and an incidence of 1/100,000 live births resulting in 37 individuals born with MLD in the US per year or 185 individuals over five years. The focus of this review is for patients with late infantile and early juvenile (pre-symptomatic and early symptomatic), which represents approximately 40-60% (74 to 111) and 35% (65) of individuals born with MLD, respectively, based on manufacturer-submitted estimates. Given that universal screening is not currently in place, it is anticipated that only a fraction of these cases will be detected. The manufacturer estimated that 32% of patients (LI: 24 to 36; EJ-PS: 21) will be detected based on a family history (i.e., children of parents who have already had an affected child), and 20% (13) of patients who are early symptomatic will be diagnosed with enough time to be eligible for treatment. Applying these sources results in estimates of 58 to 70 eligible patients in the US over five years. We used the upper end of this range, 70 patients over five years. For the purposes of this analysis, we will assume that 20% of these patients would initiate treatment in each of the five years, or 14 patients per year. It is important to note that the number of eligible patients is likely to be higher in the presence of a newborn screening program which would increase the potential budgetary impact of arsa-cel. Assuming an incidence of 1/40,000 live births, for example, suggests that the eligible patient population in the US could be as high as 91 patients per year, or 457 patients over 5 years.

The aim of the potential budgetary impact analysis is to document the percentage of patients who could be treated at selected prices without crossing a potential budget impact threshold that is aligned with overall growth in the US economy. For 2022-2023, the five-year annualized potential budget impact threshold that should trigger policy actions to manage access and affordability is calculated to be approximately $777 million per year for new drugs.[34] ICER's methods for estimating potential budget impact are described in detail in the Supplement Section F.

7.2. Results

Results showed that 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. Likewise, at the $150,000/QALY, $100,000/QALY and $50,000/QALY threshold prices ($3.2 million, $2.3 million and $1.4 million per treatment, respectively), 100% of patients could be treated with arsa-cel without reaching the potential budget impact threshold. Even with uncertainty in the exact incidence of MLD in the US, and expectations for a greater number of eligible patients if a newborn screening program is in place, our finding that 100% of patients could still be treated without reaching ICER's potential budget impact threshold is likely to still hold. The cumulative per patient potential budget impact for arsa-cel compared to usual care, and the average annual per patient budgetary impact findings using the placeholder price and the prices to reach $150,000, $100,000, and $50,000 per QALY for arsa-cel are presented in Supplement F.

Access and Affordability Alert

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.

The purpose of an ICER access and affordability alert is to signal to stakeholders and policy makers that the amount of added health care costs associated with a new service may be difficult for the health system to absorb over the short term without displacing other needed services, creating pressure on payers to sharply restrict access, or causing rapid growth in health care insurance costs that would threaten sustainable access to high-value care for all patients.

8. Policy Recommendations

Following the CTAF's deliberation on the evidence, a policy roundtable discussion was moderated by ICER's president around how best to apply the evidence on the use of arsa-cel. The policy roundtable members included two patient advocates, two clinical experts, two payers, and one representative from the drug maker. The discussion reflected multiple perspectives and opinions, and therefore, none of the statements below should be taken as a consensus view held by all participants. The top-line policy implications are presented below, and additional information can be found here.

All Stakeholders

Recommendation 1

All stakeholders have a responsibility and an important role to play in ensuring that effective new treatment options for patients with late infantile (LI) and early juvenile (EJ) metachromatic leukodystrophy (MLD) are introduced in a way that will help reduce health inequities.

The early onset forms (LI and EJ) of MLD are rapidly progressive and fatal. The disorder is rare, occurring in approximately 1 in 100,000 persons in the US.[8] Higher rates of disease occur in Navajos and Alaska Natives.[8] Because the disorder is rare, there can be delays in diagnosis, and children typically do not get diagnosed until they become symptomatic unless they have an older affected sibling. Until now, there has not been an effective treatment for this disease, and treatment consisted of supportive care only.

With the advent of an effective treatment on the horizon that is most effective in the pre-symptomatic and early symptomatic stages, access to newborn screening will become a critical step to facilitate rapid and equitable diagnosis and treatment. Delays in implementation of newborn screening for MLD will delay or deny access to treatment if children are diagnosed too late to be eligible for treatment. Thus, coordination of newborn screening will be of paramount importance as soon as arsa-cel receives FDA approval. Unfortunately, there are complex challenges in moving rapidly to broad adoption of a new newborn screening test across the US, as screening panels are decided upon at the state level. Another challenge that should be anticipated is that newborn screening is likely to turn up new genotypic variants of uncertain significance that will lead to much uncertainty about appropriate treatment and that will not fit easily within insurance coverage criteria built upon current epidemiologic data.

Finally, since MLD is a rare disease, only a few specialized centers are likely to have the expertise to offer treatment. Thus, children and their families may face geographic and financial barriers

beyond the cost of arsa-cel treatment that may widen disparities unless systematic steps are taken by insurers and others.

To address these concerns:

Policymakers managing newborn screening should take the following actions:

- Policymakers and leaders who manage state and federal procedures governing universal newborn screening should prepare to be able to offer testing for MLD as soon as the test is available. This will require that officials at the Department of Health and Human Services evaluate and add the MLD screen to the Recommended Uniform Screening Panel (RUSP) in a timely manner. In addition, state health leaders should anticipate the addition of MLD to the RUSP and be primed to offer a rapid review and approval process for adding MLD screening to state panels.

- Given the higher prevalence of MLD in the Navajo and Alaska Native populations, policymakers should ensure that tribal health services have adequate funding and other resources to offer screening and expeditious access to treatment, whether within the Indian Health Service or externally.

Payers and plan sponsors should take the following actions:

- State Medicaid payers should ensure that their specialist referral networks are adequate to ensure timely access to confirmatory testing for MLD and to treatment with arsa-cel. For a rare disease such as MLD, it will be particularly important for patients to have access to Centers of Excellence, such as Leukodystrophy Care Network Certified Centers, which will have the most experience treating MLD patients and are most likely to offer arsa-cel therapy.

- Given that most patients with MLD will need to travel to obtain treatment with arsa-cel, payers should provide wraparound coverage including transportation and housing to ensure equal access to treatment. Geographical and income constraints should not undermine the tenets of fair access to which all patients have a fundamental right.[35]

- Employers and other plan sponsors should avail themselves of re-insurance and financial protection programs offered by payers (e.g., EMBARC from Cigna[36]) to help manage the high cost of arsa-cel. Plan sponsors should not abandon coverage of gene therapies or exclude coverage for MLD specifically.

Clinicians and clinical specialty societies should take the following actions:

- Ensure that Centers of Excellence clinicians are accredited with public and private insurance plans across multiple state lines to allow patients to travel to centers with the expertise and treatment options appropriate for their situation.

- Newborn screening will generate new findings of genetic variants of unknown significance, and therefore clinical societies should foster sharing of data in a readily accessible manner (e.g., searchable online database or website) and develop guidelines to help clinicians and families navigate the uncertainty in whether newborns with uncertain findings should receive immediate treatment with arsa-cel or not.

Payers

Recommendation 1

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.

Many payers now institute "new-to-market" policies that block routine insurance coverage for new drugs for up to 180 days after FDA approval. Although in principle these blocks can be justified to allow an insurer adequate time to review the clinical evidence, discuss with clinical experts, and prepare special delivery or other policies, in practice many insurers now place new-to-market blocks on virtually any new specialty drug. In the case of arsa-cel for MLD, the evidence of transformative benefit is strong, providing assurance that FDA approval is extremely likely. Given the rapidly progressive nature of the condition and the importance of early treatment upon diagnosis, payers should recognize their responsibility to act now to ensure that coverage is ready "on day one" of FDA approval, currently anticipated in March 2024. This preparation is facilitated when manufacturers engage with payers prior to approval of their products to facilitate establishment of payment policies, much as Orchard Therapeutics has reported doing in advance of approval of arsa-cel.

Recommendation 2

Payers who serve a significant population of underserved patients should ensure that they minimize any financial barrier to treatment with arsa-cel and provide an adequate network of providers with the needed clinical expertise to support patients from diverse communities.

Since there is a higher incidence of MLD in the Navajo and Alaska Native groups, the Indian Health Service should be prepared to either establish Centers of Excellence or to establish referral pathways to other Centers of Excellence (e.g., Leukodystrophy Care Network Certified Centers) to

ensure their populations receive timely care. Additionally, given that there are likely to be few centers with the expertise to offer arsa-cel treatment, all payers should ensure that their networks either include Centers of Excellence or there are efficient mechanisms for patients and families to seek treatment at out-of-network Centers of Excellence. In particular, if single case agreements are necessary for out-of-network care, these contracts would ideally be set up proactively rather than developed as needed for individual patients, since delays in care for MLD patients can affect eligibility for treatment and impact disease-related complications.

Recommendation 3

Payers should cover fertility preservation in concert with coverage of gene therapies.

Patient stakeholders noted that future fertility is a consideration in management. There are many complex issues regarding fertility (e.g., prepubescent patients, ongoing storage). Payers should be aware that this will be discussed with patients and must be pro-active and transparent about what will be covered.

Manufacturers

Recommendation 1

Manufacturers should provide transparent, explicit justification for their pricing. To foster affordability and good access for all patients, manufacturers should align prices with the patient-centered therapeutic value of their treatments.

Drug prices that are set well beyond the cost-effective range cause not only financial toxicity for patients and families using the treatments, but also contribute to general health care cost growth that pushes families out of the insurance pool, and that causes others to ration their own care in ways that can be harmful.

Recommendation 2

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.

Although more manufacturers are engaging in developing and sharing cost-effectiveness models to assess the value of their new drugs, industry-sponsored cost-effectiveness analyses show a bias towards reporting lower incremental cost-effectiveness ratios.[37] Thus, independent value assessments are important to inform pricing and insurance coverage policies. Manufacturers

should follow the example of Orchard Therapeutics and engage with organizations that provide independent value assessments to seek a fair launch price.

Recommendation 3

Although many high-impact single and short-term therapies are good candidates for outcomes-based contracts, arsa-cel is not an ideal candidate given the very small patient population and the difficulty in framing reasonable outcome measures indicative of treatment success.

Outcomes-based contracts are increasingly being used for high-cost treatments, and are often considered for transformative gene therapies. However, use of outcomes-based contracts requires clear and achievable benchmarks. In the case of arsa-cel, it is possible that the manufacturer will pursue agreements based on engraftment. However, all patients in the clinical trials achieved full engraftment; thus, it would not be an appropriate outcome on which to base payment. Furthermore, in children with MLD treated with arsa-cel, it is not yet clear at which time points it is reasonable to measure clinically meaningful outcomes.

Patient Organizations

Recommendation 1

Patient organizations have a vital role to play to promote greater visibility for the diagnosis and treatment of MLD, including newborn screening. In addition, patient groups have a powerful voice and should apply it to create significant pressure for fair pricing and appropriate insurance coverage across all sectors of the health system.

The MLD patient community has been very active in the development of newborn screening and should continue to work with other stakeholders to implement newborn screening to facilitate the early diagnosis of MLD, now that there is an effective treatment on the horizon. Patient groups also have an ongoing responsibility to educate families about the potential risks and benefits of new therapies, particularly for the early symptomatic EJ-MLD population where there is a risk of stabilization in a worse state than prior to treatment. Furthermore, patient groups should work with other stakeholders to develop and disseminate evidence-based, balanced materials that are accessible to all patients, including those with low health literacy. Finally, patient groups should accept responsibility to publicly promote access and fair pricing of new therapies.

Researchers

Recommendation 1

With newborn screening and gene therapy on the horizon, diagnostic accuracy will be critical. An important area of focus for future research should be to continue to develop and refine biomarkers that can help predict disease type and severity.

Currently, the benefits of arsa-cel treatment appear greatest in the presymptomatic phase of the late-infantile and early juvenile forms of MLD. Therefore, early and accurate diagnosis is critical. Although there are known genotype-phenotype correlations, newborn screening will uncover new variants where type and severity of MLD will be unknown. This uncertainty will prevent some children from receiving treatment in the presymptomatic stage. While there are some data that levels of ARSA enzyme can be predictive of phenotype, continued research in this area should be a priority for researchers and funding agencies to clarify and refine this relationship such that clinicians will be able use biomarkers to help make treatment decisions. This has been successfully done in other diseases such as globoid cell leukodystrophy and would seem to be a reasonable goal for MLD as well.

References

1. 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].
2. 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.
3. 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.
4. 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.
5. Shaimardanova AA, Chulpanova DS, Solovyeva VV, et al. Metachromatic Leukodystrophy: Diagnosis, Modeling, and Treatment Approaches. *Frontiers in medicine.* 2020;7:576221-576221.
6. 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.
7. Orchard Therapeutics Highlights Recent Progress Across HSC Gene Therapy Portfolio and Outlines Key 2023 Milestones [press release]. January 9, 2023 2023.
8. MLD Foundation. Analysis of MLD Incidence & Prevalence: Domestic & Worldwide. https://MLD.foundation/Incidence. Published 2017. Updated February 2022. Accessed April 4, 2023.
9. Elgun S, Waibel J, Kehrer C, et al. Phenotypic variation between siblings with Metachromatic Leukodystrophy. *Orphanet J Rare Dis.* 2019;14(1):136.
10. Kim J, Sun Z, Ezekian B, et al. Gallbladder abnormalities in children with metachromatic leukodystrophy. *J Surg Res.* 2017;208:187-191.
11. Kehrer C, Groeschel S, Kustermann-Kuhn B, et al. Language and cognition in children with metachromatic leukodystrophy: onset and natural course in a nationwide cohort. *Orphanet J Rare Dis.* 2014;9:18.
12. Harrington M, Whalley D, Twiss J, et al. Insights into the natural history of metachromatic leukodystrophy from interviews with caregivers. *Orphanet J Rare Dis.* 2019;14(1):89.
13. Lo SH, Chang SC, Acaster S. Estimating Utility Values for Health States in Metachromatic Leukodystrophy (MLD). *Value in Health.* 2023;26(6):S345.
14. Nafees B, de Freitas H, Lloyd A, Olaye A, Pang F. A societal utility study to elicit values for stages of Metachromatic Leukodystrophy (MLD) in the United Kingdom. Virutal ISPOR Europe 2020; 2020.
15. Orchard Therapeutics. Gene Therapy for Metachromatic Leukodystrophy (MLD). Orchard Therapeutics. Clinicaltrials.gov Web site. https://classic.clinicaltrials.gov/ct2/show/NCT01560182. Published 2022. Accessed2023.
16. Orchard Therapeutics. A Safety and Efficacy Study of Cryopreserved OTL-200 for Treatment of Metachromatic Leukodystrophy (MLD). Orchard Therapeutics. Clinicaltrials.gov Web site. https://classic.clinicaltrials.gov/ct2/show/NCT03392987. Published 2022. Accessed2023.
17. Orchard Therapeutics. Orchard Therapeutics Data Submission. *Data on File.* 2023.

18. Fumagalli F, Calbi V, De Mattia F, et al. Long-term clinical outcomes of atidarsagene autotemcel (autologous hematopoietic stem cell gene therapy for metachromatic leukodystrophy) with up to 11 years follow-up. *The San Raffaele Telethon Institute For Gene Therapy.* 2023.
19. Orchard Therapeutics Presents Data from OTL-200 in Patients with Metachromatic Leukodystrophy Using Cryopreservation [press release]. 2019.
20. Trinidad M, Hong X, Froelich S, et al. Predicting disease severity in metachromatic leukodystrophy using protein activity and a patient phenotype matrix. *Genome Biol.* 2023;24(1):172.
21. Pang F, Dean R, Jensen I, Bean K, Fields C, Beckley M. The cost-effectiveness of OTL-200 for the treatment of Metachromatic Leukodystrophy (MLD) in the United States. WORLDSymposium, February 22-26; 2023; Orlando, FL.
22. FINOSE. FINOSE joint assessment report: Libmeldy (autologous CD34+ cells encoding ARSA gene). https://www.tlv.se/download/18.67f6d7817f257a5c77494a2/1646033711000/health_economic_evaluation_libmeldy_within_finose.pdf. Published 2022. Accessed May 20, 2023.
23. National Institute for Health and Care Excellence. Atidarsagene autotemcel for treating metachromatic leukodystrophy. https://www.nice.org.uk/guidance/hst18. Published 2022. Accessed May 20, 2023.
24. Institute for Clinical and Economic Review. Betibeglogene Autotemcel for Beta Thalassemia: Effectiveness and Value. *Institute for Clinical and Economic Review.* 2022.
25. Institute for Clinical and Economic Review. Gene therapies for Sickle Cell Disease. 2023.
26. Pickard AS, Law EH, Jiang R, et al. United States Valuation of EQ-5D-5L Health States Using an International Protocol. *Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research.* 2019;22(8):931-941.
27. Jiang R, Janssen MFB, Pickard AS. US population norms for the EQ-5D-5L and comparison of norms from face-to-face and online samples. *Qual Life Res.* 2021;30(3):803-816.
28. Ammann-Schnell L, Groeschel S, Kehrer C, Frölich S, Krägeloh-Mann I. The impact of severe rare chronic neurological disease in childhood on the quality of life of families-a study on MLD and PCH2. *Orphanet J Rare Dis.* 2021;16(1):211.
29. Pang F, Shapovalov Y, Howie K, Wilds A, Calcagni C, Walz M. Caregiver-reported impact on quality of life and disease burden in patients diagnosed with metachromatic leukodystrophy: Results of an online survey and a qualitative interview. 16th Annual WORLD Symposium; 2020; Orlando, FL.
30. National Institute for Health and Care Excellence. Cerliponase alfa for treating neuronal ceroid lipofuscinosis type 2. https://www.nice.org.uk/guidance/hst12. Published 2019. Accessed July 23, 2023.
31. Gissen P, Specchio N, Olaye A, et al. Investigating health-related quality of life in rare diseases: a case study in utility value determination for patients with CLN2 disease (neuronal ceroid lipofuscinosis type 2). *Orphanet J Rare Dis.* 2021;16(1):217.
32. Bean K, Olaye A, Miller B, et al. Direct cost analysis associated with the management of patients with MLD across nine European countries. ISPOR 2023; May 7-10, 2023; Boston, MA.
33. U.S. Department of Health and Human Service. Births: Provisional Data for 2021. In: Centers for Disease Control and Prevention, ed2022.
34. Institute for Clinical and Economic Review. 2020-2023 Value Assessment Framework. https://icer.org/our-approach/methods-process/value-assessment-framework/. Published 2020. Accessed.

35. Pearson SD, Towse A, Lowe M, Segel CS, Henshall C. Cornerstones of 'fair'drug coverage: appropriate cost sharing and utilization management policies for pharmaceuticals. *Journal of Comparative Effectiveness Research.* 2021;10(7):537-547.
36. Cigna. Embarc Benefit Protection. https://www.cigna.com/employers/cost-control/embarc-benefit-protection. Accessed October 4, 2023.
37. Xie F, Zhou T. Industry sponsorship bias in cost effectiveness analysis: registry based analysis. *BMJ.* 2022;377:e069573.
38. Eichler F, Sevin C, Barth M, et al. Understanding caregiver descriptions of initial signs and symptoms to improve diagnosis of metachromatic leukodystrophy. *Orphanet J Rare Dis.* 2022;17(1):370.
39. Hunter's Hope. Metachromatic Leukodystrophy. https://www.huntershope.org/family-care/leukodystrophies/metachromatic-leukodystrophy/. Published 2023. Accessed June 20, 2023.
40. CanChild. Gross Motor Function Measure (GMFM). https://canchild.ca/en/resources/44-gross-motor-function-measure-gmfm. Published 2023. Accessed.
41. Storm FA, Petrarca M, Beretta E, et al. Minimum Clinically Important Difference of Gross Motor Function and Gait Endurance in Children with Motor Impairment: A Comparison of Distribution-Based Approaches. *Biomed Res Int.* 2020;2020:2794036.
42. Kehrer C, Blumenstock G, Raabe C, Krageloh-Mann I. Development and reliability of a classification system for gross motor function in children with metachromatic leucodystrophy. *Dev Med Child Neurol.* 2011;53(2):156-160.
43. U.S. Department of Health and Human Services. Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. *National Cancer Institute.* 2017.
44. Santhanakumaran V, Groeschel S, Harzer K, et al. Predicting clinical phenotypes of metachromatic leukodystrophy based on the arylsulfatase A activity and the ARSA genotype? - Chances and challenges. *Mol Genet Metab.* 2022;137(3):273-282.
45. Biffi A, Cesani M, Fumagalli F, et al. Metachromatic leukodystrophy - mutation analysis provides further evidence of genotype-phenotype correlation. *Clin Genet.* 2008;74(4):349-357.
46. Page KM, Stenger EO, Connelly JA, et al. Hematopoietic Stem Cell Transplantation to Treat Leukodystrophies: Clinical Practice Guidelines from the Hunter's Hope Leukodystrophy Care Network. *Biol Blood Marrow Transplant.* 2019;25(12):e363-e374.
47. Wang RY, Bodamer OA, Watson MS, Wilcox WR. Lysosomal storage diseases: diagnostic confirmation and management of presymptomatic individuals. *Genet Med.* 2011;13(5):457-484.
48. 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.
49. Cook DJ, Mulrow CD, Haynes RB. Systematic reviews: synthesis of best evidence for clinical decisions. *Ann Intern Med.* 1997;126(5):376-380.
50. Higgins J, Thomas, J, Chandler, J, Cumpston, M, Li, T, Page, MJ, Welch, VA. Cochrane Handbook for Systematic Reviews of Interventions version 6.1 (updated September 2020). https://training.cochrane.org/handbook/current. Published 2020. Accessed.
51. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ.* 2021;372:n71.
52. Ollendorf D, Pearson, SD. ICER Evidence Rating Matrix: A User's Guide. https://icer.org/evidence-rating-matrix/. Published 2020. Updated January 31, 2020. Accessed.

53. Ollendorf DA, Pearson SD. An integrated evidence rating to frame comparative effectiveness assessments for decision makers. *Medical care.* 2010;48(6 Suppl):S145-152.
54. Orchard PJ. Compassionate Use of OTL-200 for Patients with Metachromatic Leukodystrophy. *19th Annual WORLDSymposium 2023.* 2023.
55. Calbi V, Fumagalli F, Gallo V, et al. Lentiviral haematopoietic stem cell gene therapy for metachromatic leukodystrophy: Results in 5 patients treated under nominal compassionate use. *Molecular Genetics and Metabolism.* 2023;138(2).
56. Bascou N, Carson V, Safonova A, Poe M, Escolar M. A prospective natural history study of metachromatic leukodystrophy: A 20 year study. *Molecular Genetics and Metabolism.* 2020;129:S26-S27.
57. Christiane K, Saskia E, Christa R, et al. Association of Age at Onset and First Symptoms With Disease Progression in Patients With Metachromatic Leukodystrophy. *Neurology.* 2021;96(2):e255.
58. Artigalás O, Lagranha VL, Saraiva-Pereira ML, et al. Clinical and biochemical study of 29 Brazilian patients with metachromatic leukodystrophy. *J Inherit Metab Dis.* 2010;33 Suppl 3:S257-262.
59. Chang S-C, Eichinger C, Field P. The natural history and burden of illness of metachromatic leukodystrophy: A systematic literature review. *Molecular Genetics and Metabolism.* 2023;138(2):107050.
60. Sanders GD, Neumann PJ, Basu A, et al. Recommendations for Conduct, Methodological Practices, and Reporting of Cost-effectiveness Analyses: Second Panel on Cost-Effectiveness in Health and Medicine. *Jama.* 2016;316(10):1093-1103.
61. Kehrer C, Blumenstock G, Raabe C, Krägeloh-Mann I. Development and reliability of a classification system for gross motor function in children with metachromatic leucodystrophy. *Dev Med Child Neurol.* 2011;53(2):156-160.
62. Elgün S, Waibel J, Kehrer C, et al. Phenotypic variation between siblings with Metachromatic Leukodystrophy. *Orphanet J Rare Dis.* 2019;14(1):136.
63. Broder MS, Quock TP, Chang E, et al. The Cost of Hematopoietic Stem-Cell Transplantation in the United States. *Am Health Drug Benefits.* 2017;10(7):366-374.
64. Centers for Medicare and Medicaid Services. FY 2023 IPPS Final Rule Home Page. https://www.cms.gov/medicare/acute-inpatient-pps/fy-2023-ipps-final-rule-home-page. Published 2023. Accessed May 20, 2023.
65. Pearson SD. The ICER Value Framework: Integrating Cost Effectiveness and Affordability in the Assessment of Health Care Value. *Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research.* 2018;21(3):258-265.

Supplemental Materials

A. Background: Supplemental Information

A1. Definitions

MLD Subtypes and Symptom Level

Late Infantile MLD (LI-MLD): Metachromatic leukodystrophy with symptom onset before 2.5 years of age. Children with LI-MLD have little or no residual ARSA activity.[5] Children with LI-MLD typically survive 5-7 years post-diagnosis with standard treatment.[38,39]

Early Juvenile MLD (EJ-MLD): Metachromatic leukodystrophy with symptom onset after 2.5 years and before 7 years of age. Children with EJ-MLD may survive 10-20 years after diagnosis.[38,39]

Pre-symptomatic MLD: Defined in trials as patients without disease-related neurological impairments, with or without signs of the disease via electroneurographic and brain MRI.[6]

Early symptomatic MLD: Defined in trials as patients with an intelligence quotient of 85 or above with the ability to walk without support but with reduced quality of performance (GMFC-MLD level 0-1, see below).[6]

Trial Outcome Measures

ARSA: Arylsulfatase A (ARSA) is an enzyme that helps breakdown sulfatides – fats in the cell membrane. In MLD, ARSA levels are lower than normal which causes an accumulation of these fats in the central and peripheral nervous systems resulting in demyelination of nerves.[6] It can be measured in the peripheral blood mononuclear cells (PBMC), or cerebrospinal fluid (CSF).

Gross Motor Function Measure (GMFM): An assessment tool measuring changes in gross motor function over time with intervention across five dimensions: 1) lying and rolling, 2) sitting, 3) crawling and kneeling, 4) standing, and 5) walking, running, and jumping. Scores range from 0 to 100 with a higher score indicating better performance.[40] In trials, an improvement of 10% between treated and natural history patients' GMFM scores was considered a clinically relevant change in response to treatment.[6,41]

Gross Motor Function Classification in MLD (GMFC-MLD): A classification of children's movements like sitting and walking ranging from level 0 where children can walk without support to level 6 where children lose all locomotion and head and trunk control.[42] See below for more detail:

GMFC-MLD Level[42]	
Level 0	Walking without support with quality of performance normal for age
Level 1	Walking without support but with reduced quality of performance, i.e. instability when standing or walking
Level 2	Walking with support. Walking without support not possible (fewer than five steps)
Level 3	Sitting without support and locomotion such as crawling or rolling. Walking with or without support not possible
Level 4	Sitting without support but no locomotion OR sitting without support not possible, but locomotion such as crawling or rolling
Level 5	No locomotion nor sitting without support, but head control is possible
Level 6	Loss of any locomotion as well as loss of any head and trunk control

GMFC: gross motor function classification

NCI CTCAE Grading:[43]

Grades	Definition
Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL†
Grade 4	Life-threatening consequences, urgent intervention indicated
Grade 5	Death related to AE

ADL: Activities of Daily Living, AE: adverse event
*Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
† Self-care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

A2. Additional Background Information

Epidemiology of MLD. MLD is diagnosed in approximately one in 40,000 to 160,000 live births worldwide.[1] 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).[1]

Adult onset MLD. The least common form is the adult type, which develops after 16 years of age and is associated with slower progression of symptoms and longer survival (20-30 years) after diagnosis.[3] In adults, MLD manifests as cognitive decline and behavioral and psychiatric problems such as depression and psychosis, which can lead to problems with work or school; drug or alcohol misuse are also common.[1]

Diagnosis and clinical course of MLD. Diagnosis of MLD is made based on a combination of urinary, blood, and genetic testing, including ARSA levels, urinary sulfatides, and genetic mutation testing. In some cases, the combination of ARSA activity in peripheral blood cells and ARSA genotype may be predictive of age of onset and disease progression – for example, residual ARSA enzyme activity of less than 1% is associated with early onset MLD and more rapid disease progression.[44] While age of onset and progression are similar in children with LI-MLD, there is more variability in juvenile MLD, although disease course in siblings is more similar than in unrelated children.[9] There appears to be some correlation between genotype, age of onset, and disease progression[45]. Newer studies suggest a high genotype-phenotype correlation[20]; however, there may be less common mutations or compound heterogeneity (combination of different mutations) where correlation may be somewhat less.[44]

Children with MLD start with normal development. As sulfatides accumulate in the body, children have a period of developmental stagnation, which then proceeds to progressive neurological impairment, with symptoms and speed of progression dependent on the form of the disease. For example, children with LI-MLD begin to miss or lose motor and cognitive milestones and then progress to muscle weakness, spasticity, loss of swallowing and speaking, loss of vision, and eventually difficulty breathing. The juvenile form often presents with difficulties in school due to behavioral and cognitive problems such as inability to pay attention and learn new skills. Motor symptoms include difficulty walking, loss of sensation, and spasticity, and, as in the late infantile form, difficulty with eating, speaking, and breathing mark late manifestations of the disease.[1] Progression of disease is faster in the early onset forms of the disease and disease course is more variable in the later onset forms.

A3. Potential Cost-Saving Measures in MLD

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 headroom in health care budgets for higher-value innovative services (for more information, see https://icer.org/our-approach/methods-process/value-assessment-framework/). These services are ones that would not be directly affected by therapies for MLD (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. During stakeholder engagement and public comment periods, ICER encouraged all stakeholders to suggest services (including treatments and mechanisms of care) currently used for patients with MLD that could be reduced, eliminated, or made more efficient. Clinical experts emphasized that hematopoietic stem cell transplant (HSCT) is not an effective treatment for LI-MLD or EJ-MLD, given the rapid progression of disease. However, some children with LI and EJ-MLD are still being referred for HSCT. Ineffective HSCT should be avoided.

B. Patient Perspectives: Supplemental Information

B1. Methods

To gather stakeholder perspectives for this report, we interviewed patients, patient groups, clinicians, and the manufacturer.

We interviewed a total of eight caregivers, all parents of children living with MLD in the US. Two parents were referred to us from clinical experts, four parents were referred by patient organizations, and two parents submitted comments on ICER's "Share Your Story" form on the ICER website.

We interviewed three patient groups, both groups specific to MLD and more general to leukodystrophies.

We interviewed six clinical experts in MLD, genetics, and HSCT from the US and Europe. Clinical experts were referred to us by the manufacturer, patient organizations, and other clinical experts. Clinical experts described the devastating impact of late infantile and early juvenile MLD on children and families, and that gene therapy was a promising treatment. Some clinical experts offered HSCT to patients based on individual circumstances; others were not convinced about the efficacy of HSCT in this population.

C. Clinical Guidelines

Hunter's Hope Leukodystrophy Care Network Guidelines: Stem Cell Transplantation to Treat Leukodystrophies: Clinical Practice Guidelines[46]

These guidelines were developed by the Treatment Clinical Practice Guidelines Working Group of the Leukodystrophy Care Network, including a committee of parents with children affected by leukodystrophies. The guidelines encompass both disease-specific and general leukodystrophy care. For MLD, the guidelines recommend that diagnostic evaluation should include neuroimaging, cognitive testing, and neurophysiologic testing to determine disease status, as well as gallbladder imaging. In terms of treatment with HSCT, the guidelines state that children with symptomatic LI-MLD and older patients with advanced disease are unlikely to benefit from HSCT, and supportive care to manage symptoms is recommended. For patients who do undergo HSCT, the guidelines recommend comprehensive monitoring for graft versus host disease (GVHD), organ dysfunction, and other complications, as well as aggressive physical and occupational therapy to preserve function.

American College of Medical Genetics Guidelines: Lysosomal Storage Diseases Diagnostic Confirmation & Management of Presymptomatic Individuals[47]

The American College of Medical Genetics published guidelines on the diagnosis and management of lysosomal storage diseases including MLD in 2011. The guidelines state that both analysis of urinary sulfatides and *ARSA* gene sequencing are required to confirm diagnosis. Presymptomatic children with MLD should be followed by both a neurologist and a metabolic physician and have periodic brain MRI to monitor the status of central nervous system demyelination. In terms of treatment, children with late infantile MLD should be offered palliative and supportive care to prevent or delay secondary complications; HSCT is not effective or recommended for LI-MLD, even at the presymptomatic stage. Patients with juvenile and adult onset MLD should be referred for HSCT evaluation, though it has substantial risks and unknown long-term effects. HSCT is best performed before onset of clinical symptoms to stabilize demyelination and stop or slow disease progression in the central nervous system; however, it does not stop disease progression in the peripheral nervous system and peripheral neuropathy may develop even years after successful HSCT.

D. Comparative Clinical Effectiveness: Supplemental Information

D1. Detailed Methods

PICOTS

In line with the above research questions, the following specific criteria have been defined utilizing PICOTS (Population, Interventions, Comparisons, Outcomes, Timing, Setting and Study Design) elements.

Population

The populations of focus for this review were:

- 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 [GMFC-MLD] score of ≤1) and with preserved cognition (intelligence quotient [IQ] score of ≥85).

Interventions

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

Comparators

We compared 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 did not 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 were 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,[48] 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, GMFC-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 was derived from studies of any duration.

Settings

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

Table D1.1. PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Reported on Page #
TITLE			
Title	1	Identify the report as a systematic review.	
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	
METHODS			
Eligibility Criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	
Information Sources	6	Specify all databases, registers, websites, organizations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	
Search Strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	
Selection Process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	
Data Collection Process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	
Data Items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	
Study Risk of Bias Assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	

Effect Measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	
Synthesis Methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	
Reporting Bias Assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	
Certainty Assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	
RESULTS			
Study Selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	
Study Characteristics	17	Cite each included study and present its characteristics.	
Risk of Bias in Studies	18	Present assessments of risk of bias for each included study.	
Results of Individual Studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	
Results of Syntheses	20a	For each synthesis, briefly summarize the characteristics and risk of bias among contributing studies.	
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g., confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	
Reporting Biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	

Certainty of Evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	
	23b	Discuss any limitations of the evidence included in the review.	
	23c	Discuss any limitations of the review processes used.	
	23d	Discuss implications of the results for practice, policy, and future research.	
OTHER INFORMATION			
Registration and Protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	
Competing Interests	26	Declare any competing interests of review authors.	
Availability of Data, Code, and Other Materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	

From: Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *PLoS Med.* 2021;18(3):e1003583

Data Sources and Searches

Procedures for the systematic literature review assessing the evidence on new therapies for MLD followed established best research methods.[49,50] We conducted the review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[51] The PRISMA guidelines include a checklist of 27 items (see Table D1).

We searched MEDLINE, EMBASE, Cochrane Database of Systematic Reviews, and Cochrane Central Register of Controlled Trials for relevant studies. Each search was limited to English-language studies of human subjects and excluded articles indexed as guidelines, letters, editorials, narrative reviews, or news items. We included abstracts from conference proceedings identified from the systematic literature search. All search strategies were generated utilizing the Population, Intervention, Comparator, and Study Design elements described above. The proposed search strategies included a combination of indexing terms (MeSH terms in MEDLINE and EMTREE terms in EMBASE), as well as free-text terms.

To supplement the database searches, we performed manual checks of the reference lists of included trials and systematic reviews and invited key stakeholders to share references germane to the scope of this project. We also supplemented our review of published studies with data from conference proceedings, regulatory documents, information submitted by manufacturers, and other grey literature when the evidence met ICER standards (for more information, see the Policy on Inclusion of Grey Literature in Evidence Reviews).

Table D1.2. Search Strategy of Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, Ovid MEDLINE and Versions(R) 1946 to Present and Cochrane Central Register of Controlled Trials

#	Search Terms
1	exp metachromatic leukodystrophy/
2	("Adult Metachromatic Leukodystroph*" or "Adult-Type Metachromatic Leukodystroph*" or "ARSA Deficienc*" or "Arylsulfatase A Deficienc*" or "Cerebral sclerosis, Diffuse, Metachromatic Form" or "Cerebroside Sulfatase Deficienc*" or "Cerebroside Sulphatase Deficiency Disease" or "Deficiencies, ARSA" or "Deficiencies, Cerebroside Sulfatase" or "Deficiency, ARSA" or "Deficiency, Arylsulfatase A" or "Deficiencies, Arylsulfatase A" or "Deficiency, Cerebroside Sulfatase" or "Greenfield Disease" or "Greenfield's Disease" or "Infant Metachromatic Leukodystroph*" or "Infant-Type Metachromatic Leukodystroph*" or "Juvenile Metachromatic Leukodystroph*" or "Juvenile-Type Metachromatic Leukodystroph*" or "Leukodystrophies, Adult Metachromatic" or "Leukodystrophies, Adult-Type Metachromatic" or "Leukodystrophies, Juvenile Metachromatic" or "Leukodystrophies, Juvenile-Type Metachromatic" or "Leukodystrophies, Metachromatic" or "Leukodystrophy, Adult Metachromatic" or "Leukodystrophy, Adult-Type Metachromatic" or "Leukodystrophy, Juvenile Metachromatic" or "Leukodystrophy, Juvenile-Type Metachromatic" or "Leukodystrophy, Metachromatic, Adult" or "Leukodystrophy, Metachromatic, Juvenile" or "Leukoencephalopathies, Metachromatic" or "Leukoencephalopathy, Metachromatic" or "Lipidosis, Sulfatide" or "Metachromatic Leukodystroph*" or "Metachromatic Leukoencephalopath*" or "Sulfatase Deficiencies, Cerebroside" or "Sulfatase Deficiency, Cerebroside" or "Sulfatide Lipidosis").ti,ab.

3	1 OR 2
4	('atidarsagene autotemcel' OR 'gsk 2696274' OR 'gsk2696274' OR 'libmeldy' OR 'otl 200' OR 'otl200' OR 'otl-200').ti,ab.
5	('natural history').ti,ab.
6	(3 AND 4) OR (3 AND 5)
7	(animals not (humans and animals)).sh.
8	6 NOT 7
9	(addresses OR autobiography OR bibliography OR biography OR comment OR congresses OR consensus development conference OR dictionary OR directory OR duplicate publication OR editorial OR encyclopedia OR festschrift OR guideline OR interactive tutorial).pt
10	8 NOT 9
11	limit 10 to English language
12	Remove duplicates from 11

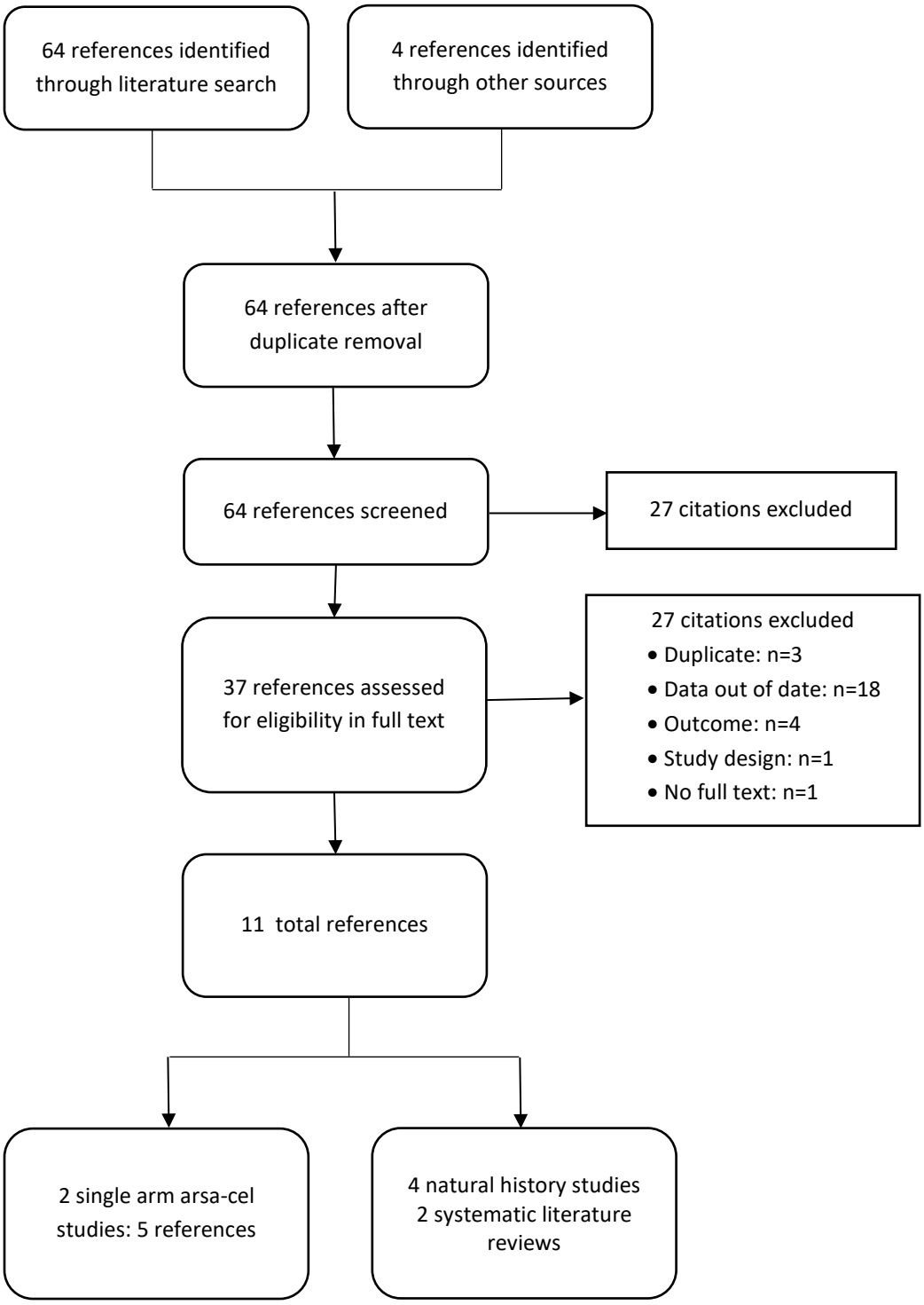
Search last ran on August 15, 2023

Table D1.3. Search Strategy of EMBASE

#	Search Terms
1	'metachromatic leukodystrophy'/exp
2	'cerebroside sulfatase deficiency syndrome':ti,ab OR 'cerebroside sulfate storage disease':ti,ab OR 'cerebroside sulphate storage disease':ti,ab OR 'infantile metachromatic leucodystrophy':ti,ab OR 'infantile metachromatic leukodystrophy':ti,ab OR 'late infantile metachromatic leucodystrophy':ti,ab OR 'late infantile metachromatic leukodystrophy':ti,ab OR 'leucodystrophy, metachromatic':ti,ab OR 'leukodystrophy, metachromatic':ti,ab OR 'lipidosis, sulfatide':ti,ab OR 'lipidosis, sulphatide':ti,ab OR 'mckusick 250*0':ti,ab OR 'metachromatic leucodystrophy':ti,ab OR 'metachromatic leucodystrophy, infantile':ti,ab OR 'metachromatic leucodystrophy, late infantile':ti,ab OR 'metachromatic leucoencephalopathy':ti,ab OR 'metachromatic leukodystrophy, infantile':ti,ab OR 'metachromatic leukodystrophy, late infantile':ti,ab OR 'metachromatic leukoencephalopathy':ti,ab OR 'metachromatic leukoencephaly':ti,ab OR 'metachromic leucodystrophy':ti,ab OR 'sulfatide lipidosis':ti,ab OR 'sulfatidosis':ti,ab OR 'sulphatide lipidosis':ti,ab
3	#1 OR #2
4	'atidarsagene autotemcel'/exp
5	'gsk 2696274':ti,ab OR 'gsk2696274':ti,ab OR 'libmeldy':ti,ab OR 'otl 200':ti,ab OR 'otl200':ti,ab OR 'otl-200':ti,ab
6	#4 OR #5
7	'natural history':ti,ab
8	(#3 AND #6) OR (#3 AND #7)
9	('animal'/exp OR 'nonhuman'/exp OR 'animal experiment'/exp) NOT 'human'/exp
10	#8 NOT #9
11	#10 AND [english]/lim
12	#11 AND [medline]/lim
13	#11 NOT #12
14	#13 AND ('chapter'/it OR 'conference review'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it OR 'review'/it OR 'short survey'/it)
15	#13 NOT #14

Search last ran on August 15, 2023

Figure D1.1. PRISMA Flow Chart Showing Results of Literature Search for Arsa-cel and Natural History Cohort



Study Selection

We performed screening at both the abstract and full-text level. Two investigators independently screened all titles and abstracts identified through electronic searches according to the inclusion and exclusion criteria described earlier using Nested Knowledge; a third reviewer worked with the initial two reviewers to resolve any issues of disagreement through consensus. We did not exclude any study at abstract-level screening due to insufficient information. For example, an abstract that did not report an outcome of interest would be accepted for further review in full text. We retrieved the citations that were accepted during abstract-level screening for full text appraisal. One investigator reviewed full papers and provided justification for exclusion of each excluded study.

Data Extraction

Data were extracted into Excel. The basic design and elements of the extraction forms followed those used for other ICER reports. Elements included a description of patient populations, sample size, duration of follow-up, funding source, study design features, interventions (agent, dosage, frequency, schedules), concomitant therapy allowed and used (agent, dosage, frequency, schedules), outcome assessments, and results. The data extraction was performed in the following steps:

1. One reviewer extracted information from the full articles, and a second reviewer validated the extracted data.
2. Extracted data were reviewed for logic, and a random proportion of data were validated by a third investigator for additional quality assurance.

Assessment of Level of Certainty in Evidence

We used the ICER Evidence Rating Matrix to evaluate the level of certainty in the available evidence of a net health benefit among each of the interventions of focus (see Appendix D).[52,53]

Assessment of Bias

We evaluated the evidence base for the presence of potential publication bias. Given the emerging nature of the evidence base for newer treatments, we performed an assessment of publication bias using ClinicalTrials.gov. Search terms included "atidarsagene autotemcel", "OTL-200", and "metachromatic leukodystrophy." We selected studies which would have met our inclusion criteria and for which no findings have been published. We provided qualitative analysis of the objectives and methods of these studies to ascertain whether there may be a biased representation of study results in the published literature.

Data Synthesis and Statistical Analyses

Relevant data on key outcomes of the main studies were summarized narratively in the body of the review and in evidence tables (see Supplement Section D3). Key differences between the studies in terms of the study design, patient characteristics, outcomes, and study quality were explored in the text of the report. The feasibility of conducting a quantitative synthesis was evaluated by looking at trial design, populations, analytic methods, and outcome assessments across outcomes of interest in the arsa-cel trials. The manufacturer submitted integrated analyses from all patients enrolled in the clinical trials, expanded access frameworks, and compassionate use programs. Thus, we did not pursue independent quantitative synthesis of the data.

D2. Additional Clinical Evidence

Evidence Base

Data from all published studies and presentations are presented in this section. We also discussed additional endpoints that were measured in Phase I/II and Phase II trials to assess the effect of arsa-cel in preventing neurological manifestations of MLD such as damage to the nerves and white matter of the brain. Trials also assessed arsa-cel's ability to prevent progression of motor function via the Gross Motor Function Classification (GMFC) measure.

In the Phase I/II trial, there was an exploratory analysis of 12 patients in the ITT analysis who were treated with arsa-cel and 11 siblings in the natural history cohort (one patient in the natural history cohort was the sibling match for two treated patients). The set was used to compare effects of arsa-cel with natural history in patients with a lower level of variability in clinical progression.[6]

Additional information was retrieved from two compassionate use programs, one from US with three patients and another from Italy with five patients.[54,55]

Additional Clinical Benefits

GMFM-88 score

A co-primary endpoint in the Phase I/II trial was a ≥10% improvement in mean GMFM-88 total score between the treated patients and those in the natural history cohort at 24 months. Findings from the published study suggested that the treatment difference between treated and untreated patients reached statistical significance for those with both pre-symptomatic LI and pre-symptomatic EJ-MLD. Patients with early symptomatic EJ- MLD patients experienced numerical improvements in GMFM-88 total score at 24 months in the Phase I/II publication, although not as large as the presymptomatic population and the differences were not statistically significant in this population. However, in the data submitted by the manufacturer, statistical significance was

observed for early symptomatic EJ-MLD patients. Overall, available data suggest that all arsa-cel treated patients regardless of subtypes continued to have higher GMFM-88 scores in the long term, compared with natural history subjects, who inevitably progress to more severe disease without treatment.[17] See Supplement Table D3.4 to D3.6 for more detail.

ARSA Activity Levels

A key co-primary endpoint of Phase I/II trial was the PBMC ARSA level change from baseline to 24 months post treatment. An estimated 18.7-fold increase (95% CI 8.3 to 42.2, P <0.0001) from baseline in PBMC ARSA activity was observed among the LI-MLD patients at 24 months. EJ-MLD patients had a 5.7 fold increase (95% CI 2.6 to 12.4, P <0.0001); data stratified by pre-symptomatic and early symptomatic EJ-MLD were not available for this outcome.[6] For all three subtypes of MLD (n=37), the ARSA activity level in cerebrospinal fluid (CSF) remained within the normal range for up to eight years after treatment.[18]

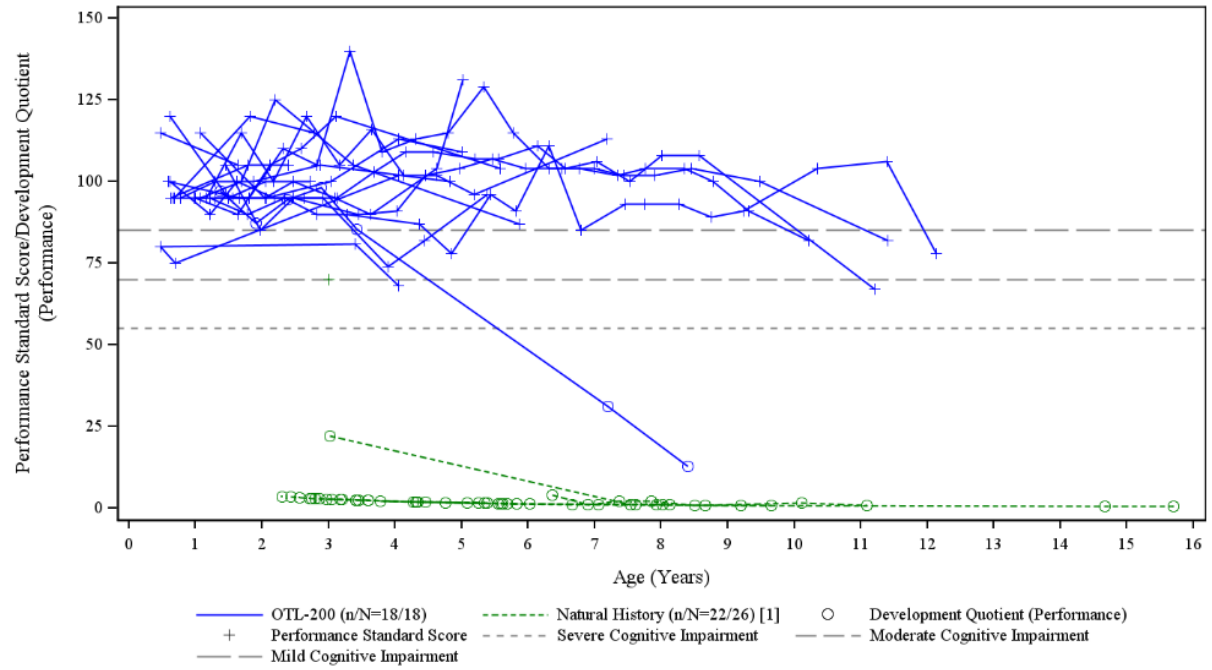
GMFC-MLD

Almost all the arsa-cel treated presymptomatic LI and EJ-MLD patients remained in early stage MLD with a GMFC-MLD level of 0 to 2 at their last follow-up; one patient in PS LI-MLD group and two patients in ES EJ-MLD group had progressed to GMFC-MLD level 5 or above. In contrast, 70% of the LI-MLD patients in the natural history cohort (n=19) had already died at their last follow-up, while the rest had progressed to GMFC level 5 or above. The majority of treated early symptomatic EJ-MLD patients were between GMFC-MLD level 0 and 4 at last follow-up. However, around two-thirds of the EJ-MLD in the natural history cohort were already in GMFC level 5 or above at last follow-up.[18] See Supplement Table D3.8 for more detail.

Cognitive Function

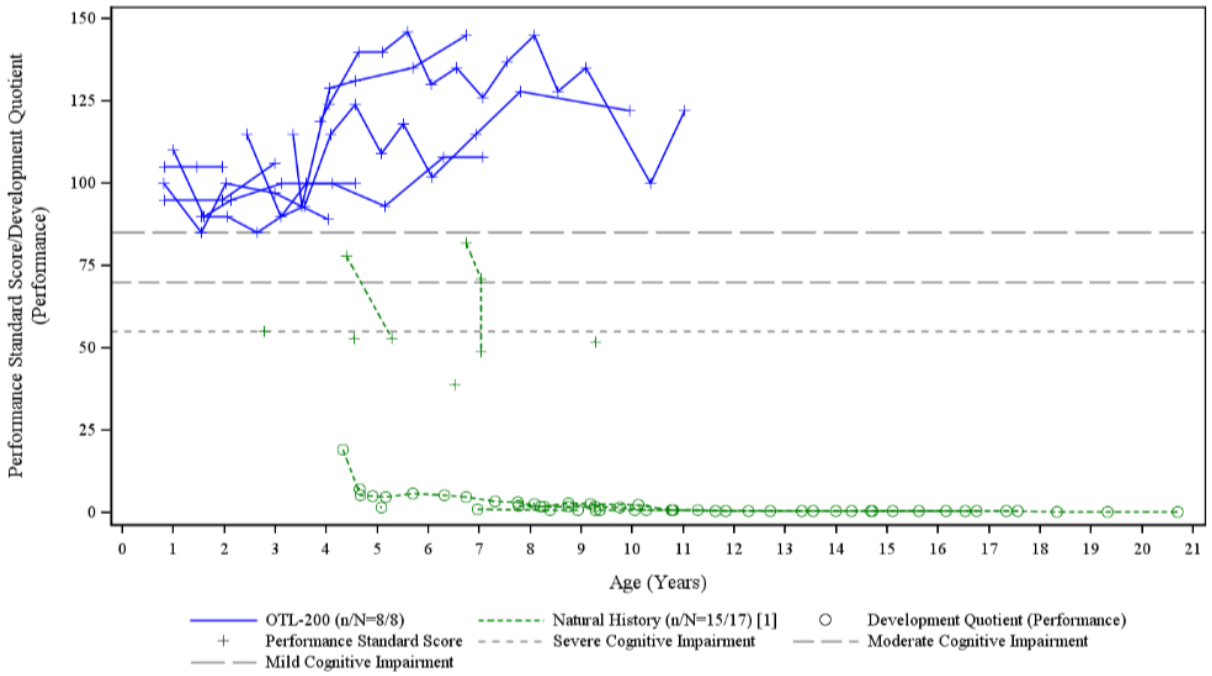
Cognitive function was assessed using measures known as the Performance Standard Score (PSS) and Development Quotient Performance (DQp). Children with normal cognitive function or mild cognitive impairment have PSS/DQp scores above 70. Those with moderate cognitive impairment have scores between 55 and 70 and those with severe cognitive impairment have scores of below 55. Overall, patients with presymptomatic LI, presymptomatic and early symptomatic EJ MLD who were assessed for cognitive function showed preservation of function (PSS/DQp>70) throughout follow-up as compared with children in the natural history cohort who experienced severe cognitive decline (PSS/DQp>55).[17] See Figures D2.1-D2.3 below for patient-level results stratified by MLD subtype.

Figure D2.1. Performance Standard Score/Development Quotient vs. Age (Years) for Presymptomatic Late Infantile MLD[17]



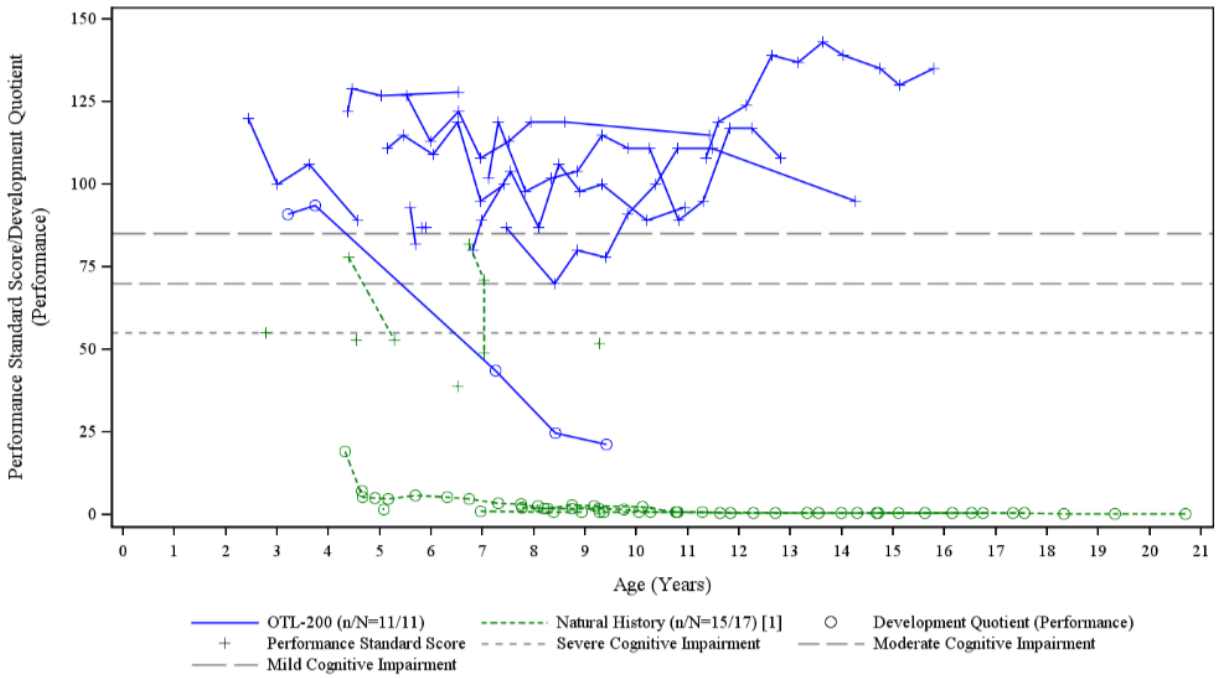
Note: This figure comes directly from Orchard Therapeutics Data on File.

Figure D2.2. Performance Standard Score/Development Quotient vs. Age (Years) for Presymptomatic Early Juvenile MLD[17]



Note: This figure comes directly from Orchard Therapeutics Data on File.

Figure D2.3. Performance Standard Score/Development Quotient vs. Age (Years) for Early Symptomatic Early Juvenile MLD[17]



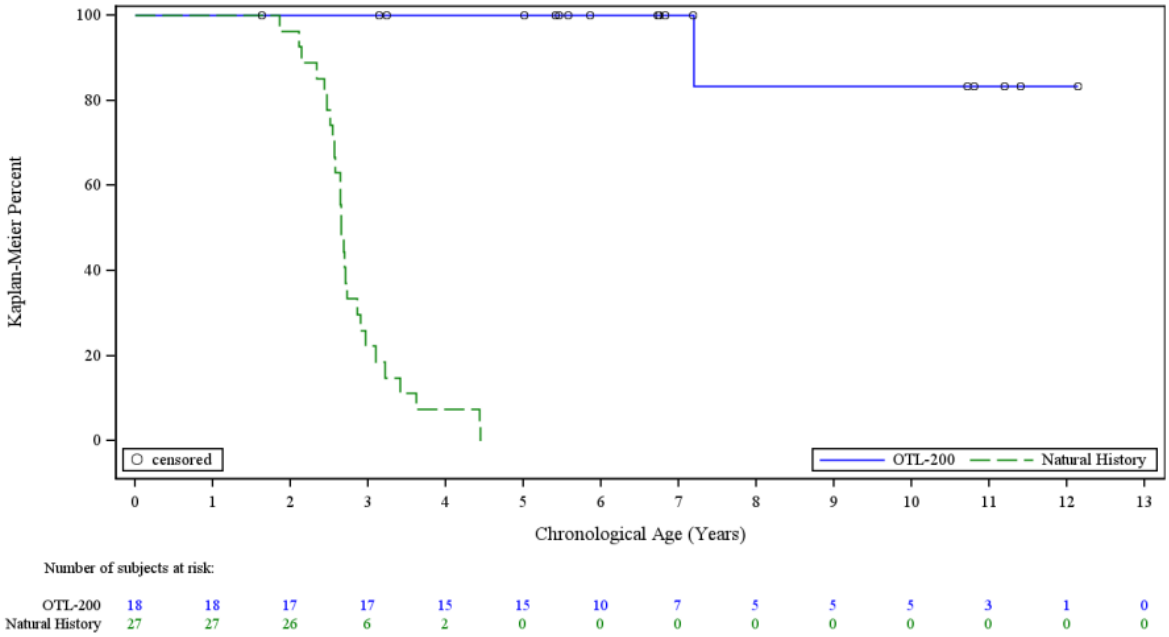
Note: This figure comes directly from Orchard Therapeutics Data on File.

Time to GMFC-MLD Level Progression

Participants from the Phase I/II and Phase II trials were also assessed for how long it took to progress to a subsequent GMFC level: level 2 (loss of independent ambulation), level 3 (loss of walking), level 5 (loss of locomotion and sitting without support) or death. Overall, patients in the natural history cohort progressed to the next GMFC level more rapidly than those treated with arsa-cel.[17] See Supplement Table D3.9 to D3.11 for more detail.

Patients who did not progress to GMFC level 5 or higher (meaning they still maintained either the ability to sit without support or locomotion such as crawling or rolling) were considered to have reached "severe motor impairment-free survival". Overall, there was a statistically significant difference in severe motor impairment free survival between the arsa-cel treated and natural history cohort LI-MLD patients (P<0.001). The arsa-cel treated LI MLD patients remained free from severe motor impairment at 4.5 years of chronological age. By chronological age seven, the probability of severe motor free impairment was 0.83 and this probability remained stable to year 12 of follow-up.[18] In the natural history cohort, all LI-MLD patients progressed to GMFC level 5 or above by 4.5 years of age.[6] See Figure D2.4.

Figure D2.4. Severe Motor Impairment Free Survival in Presymptomatic LI versus LI Natural History Cohort [17]



For children with EJ-MLD, a statistically significant difference in severe motor impairment free survival was also observed between children treated with arsa-cel and those in the natural history cohort (P=0.049 for presymptomatic EJ-MLD patients and P<0.001 for early symptomatic EJ-MLD patients).[18] See Figure D2.5. and D2.6.

Data submitted by the manufacturer showed children with EJ-MLD in the natural history cohort progressed to GMFC level 5 or higher at around 10 years of chronological age whereas most arsa-cel treated patients remained below this GMFC level at that point (severe motor impairment-free survival probability in presymptomatic EJ-MLD: 0.88 and early symptomatic EJ-MLD: 1.00). Additionally, presymptomatic EJ- MLD patients sustained this level of event-free survival until the time of last follow-up at 11 years of chronological age while the proportion of early symptomatic EJ-MLD patients with event-free survival declined to 58% at 16 years of chronological age and remained there until the time of latest follow up (i.e., 19 years of chronological age).[17] See Supplement Table D3.11 for more detail.

Figure D2.5. Severe Motor Impairment Free Survival in Presymptomatic EJ versus EJ Natural History Cohort [17]

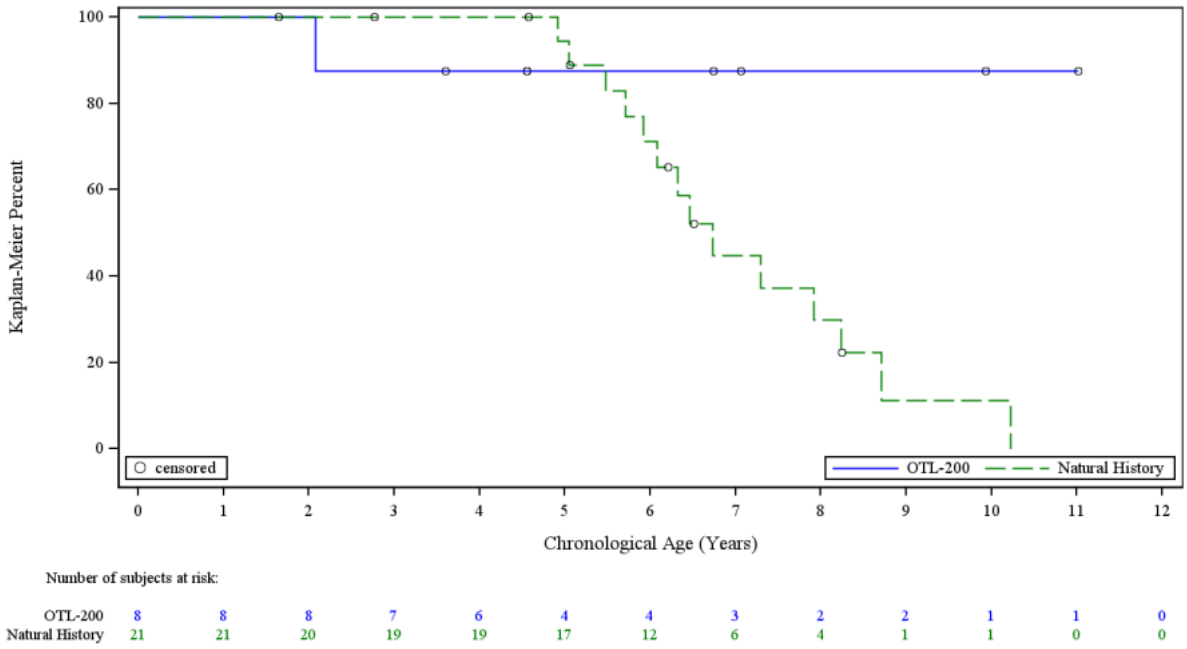
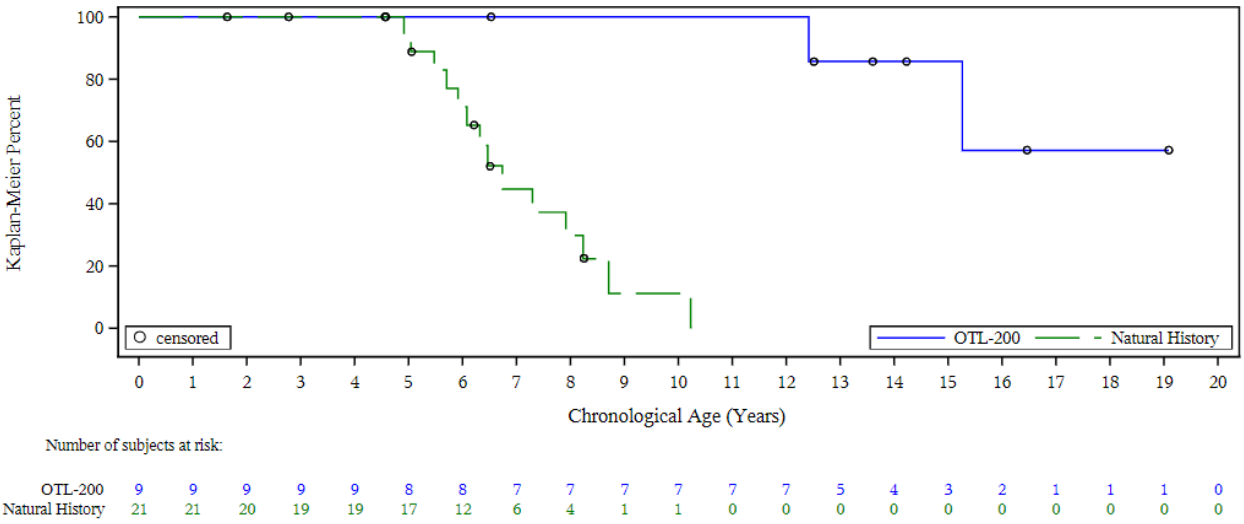


Figure D2.6. Severe Motor Impairment Free Survival in Early Symptomatic EJ versus EJ Natural History Cohort [17]



Note: Two patients in the early-symptomatic early juvenile (EJ)-MLD arsa-cel treated group who died due to disease progression before the 2-year follow-up time and were excluded from this survival analysis as they did not meet revised protocol inclusion criteria.

Nerve Conduction Velocity

A nerve conduction velocity (NCV) test was used to assess damage to peripheral nerves responsible for muscle function, movement, and processing of sensory information. Patients with late-infantile MLD treated with arsa-cel in the Phase I/II trial showed significantly less nerve damage than those in the natural history cohort at up to three years of follow-up (Supplement Table D3.13). In patients with EJ-MLD, peripheral nerve function was more heterogeneous and could not be compared in treated and untreated patients due to heterogeneity of baseline nerve conduction velocity between the two groups.[6]

Total Brain MRI Score

Participants in the Phase I/II trial underwent brain MRI to assess the amount of white matter involvement or atrophy, reported as the brain MRI total score. All patients treated with arsa-cel whose brain MRIs were assessed (n=19) had significantly lower brain MRI total scores, indicating less white matter involvement and damage, than patients in the natural history cohort after up to three years of follow-up regardless of MLD subtype (mean total MRI severity score: LI MLD 3.6 versus 21.7, $p<0.0001$; EJ MLD 10.1 versus 20.5, $p=0.004$)[6]. See Supplement Table D3.13 for more detail.

Additional Harms

The Phase I/II trial reported late harms related to the arsa-cel with a median follow-up of three years (range 0.64 to 7.51 years). Four patients experienced delayed platelet engraftment which resolved later and there was one case of prolonged anemia and thrombocytopenia that resulted in the use of back-up hematopoietic stem cells. More than half of the patients (15 out of 29) in the Phase I/II trial including EAFs and CUPs experienced gait disturbance that may have been related to MLD progression. Additional common post gene therapy adverse events include motor dysfunction (31%), muscle spasticity (31%), aphasia (21%), and ataxia (17%), although these symptoms may have been due to progression of MLD rather than adverse events from treatment. No malignancies, bone marrow abnormalities, clonal expansion, and replication-competent lentivirus were observed.[6] The only treatment-related harms experienced by arsa-cel treated patients (n=39) were anti-ARSA antibodies observed in six patients and most cases resolved either spontaneously or after a short course of rituximab.[18] See Supplement Table D3.14.

Subgroup Analyses

An exploratory subgroup analysis of 12 treated patients and their untreated siblings showed similar findings to the main analysis in terms of severe motor impairment-free survival in both LI and EJ-MLD patients.[6]

Compassionate Use Program in United States

There were an additional eight patients who received treatment with arsa-cel through a Compassionate Use Program not included in the Phase I/II and phase II trials. Five patients with presymptomatic LI-MLD were treated under a Milan-based Compassionate Use Program at a median age of 11 months. All patients successfully engrafted arsa-cel and restored ARSA activity levels in PBMCs to supranormal levels by 30 days post-treatment. ARSA activity levels were sustained in all patients. Patients continued to acquire new motor and cognitive skills and only experienced harms related to myeloablative busulfan conditioning.[55] The remaining three patients with MLD, one child with each subtype, were treated through a United States-based Compassionate Use Program. All three patients also successfully engrafted arsa-cel and increased ARSA activity levels in PBMCs to normal or supranormal levels shortly after infusion. After one year of follow-up, all patients were living and had maintained ARSA activity levels. There was no evidence of malignancies.[54]

Natural History Studies

We found a total of five natural history studies during our systematic review, which are summarized here. A semi-structured interview with MLD caregivers (i.e., parents) provided meaningful insights into the natural history of MLD. The study was conducted in the US with a total of 32 caregivers of patients with LI and juvenile MLD. The interview highlighted the differences between the two subtypes and suggested that significant interindividual variability exists.[12] Bascou et al. conducted a US-based prospective natural history study of MLD patients (n=122) with 20 years of follow-up. The median age of diagnosis was 34 months and almost two-thirds of the patients had experienced symptom onset between birth and 36 months. For LI and EJ-MLD, early symptoms were primarily motor impairments; cognitive symptoms were predominant in late juvenile and adult forms of MLD.[56] The largest natural history study outside of US was conducted in Germany, including 97 MLD patients (35 LI and 18 EJ MLD). Findings from this study supported that both onset age and type of first symptoms predicts disease progression in MLD patients[57] Another study from Brazil from 2010 included 24 LI-MLD patients and 4 juvenile MLD patients. The median age at onset of diagnosis was 34 months for LI-MLD patients and 118 months for juvenile MLD. No correlation between ARSA activity in leukocytes and clinical form of the disease was found during the time of the study.[58]. Finally, a systematic literature review including 120 studies was conducted in 2021 to understand

the natural history of late-infantile and juvenile MLD patients. The symptomatic onset age ranged between 0.5 to three years for late-infantile and two to 16 years for juvenile MLD patients. In addition, the late-infantile patients had faster decline in their motor function and lower survival rate compared to the juvenile MLD patients. Overall, these natural history studies were not significantly different from the natural history study presented in the manufacturer's data.[59]

D3. Evidence Tables

Table D3.1. Study Design of Key Trials of Arsa-cel

Trial	Study Design	Treatment Arm	Inclusion & Exclusion Criteria	Key Outcomes [Timepoint]
Phase II[16]* NCT03392987	Single-arm, open-label, clinical trial N=10 Setting: Milan, Italy	Intravenous (IV) infusion of OTL-200 gene therapy following conditioning regimen with busulfan	**Inclusion:** - Diagnosis of MLD, based on ARSA activity AND - Child has an older sibling affected by MLD with age of symptom onset ≤6 years of age OR - A pre-symptomatic child without an older affected sibling has strong evidence of an early onset variant of MLD, and the subject is ≤6 years of age. **Exclusions:** - Has undergone allogeneic hematopoietic stem cell transplantation and has evidence of residual cells of donor origin AND - Delay in expected achievement of independent standing or independent walking, together with abnormal signs at neurological evaluation OR - Documented neurological signs and symptoms of MLD associated with cognitive, motor, or behavioral functional impairment or regression.	- Change in Gross Motor Function Measure (GMFM) score [at 24 months post gene-therapy]
Phase I/II[15] NCT01560182	Single-arm, open-label, clinical trial N=20 Setting: Milan, Italy	Intravenous (IV) infusion of OTL-200 gene therapy following conditioning regimen with busulfan	**Inclusion:** - Age of symptom onset up to 7 years AND - Pre-symptomatic MLD patients with the late infantile variant OR - Pre- or early symptomatic MLD patients with the early juvenile variant **Exclusion:** - Has undergone allogeneic hematopoietic stem cell transplantation in the previous 6 months and has evidence of residual cells of donor origin.	- Improvement of Gross Motor Function Measure (GMFM) score [24 months] - Increase of residual Arylsulfatase A (ARSA) Activity [24 months] - Safety related to conditioning regimen and lentiviral transduced cell infusion

ARSA: arylsulfatase A, GMFM: Gross motor function measure, MLD: metachromatic leukodystrophy, N: total number

* This trial is currently ongoing with study completion expected in April 2028.

Table D3.2. Baseline Characteristics

Trial		Phase I/II, Phase II, Expanded Access Programs*[17,18]				
MLD Subtype		Late Infantile		Early Juvenile		
Arms		Pre-symptomatic Arsa-cel	Natural History	Pre-symptomatic Arsa-cel	Early Symptomatic Arsa-cel	Natural History
N		18	26	8	9	17
Median Follow-Up, years (range)		6.09 (2.41-11.03)	4.44 (0.63-18.85)	3.34 (1.14-8.37)	7.20 (0.64-9.19)	5.56 (0.38-20.73)
Age†, years	Mean (SD)	0.96 (0.28)	1.75 (0.32)	1.98 (1.26)	5.49 (2.62)	4.06 (1.56)
	Median (range)	0.86 (0.63-1.48)	1.57 (1.21-2.33)	1.34 (0.94-4.08)	5.75 (2.54-11.64)	4.38 (1.60-6.18)
Sex, n (%)	Female	5 (28)	14 (54)	2 (25)	3 (33)	9 (53)
	Male	13 (72)	12 (46)	6 (75)	6 (66)	8 (47)
Race, n (%)	White (Caucasian)	13 (72)	23 (88)	6 (75)	9 (100)	16 (94)
	White (Arabic or North African heritage)	3 (17)	3 (12)	1 (13)	0	1 (6)
	Black/African American	0	0	1 (13)	0	0
	Asian	2 (12)	0	0	0	0

ES: early symptomatic, n: number, N: total number, NR: not reported, PS: pre-symptomatic, SD: standard deviation, %: percent

* The total sample size was 39. One LI and one EJ were excluded because of entering a rapidly progressive phase and additional two early symptomatic EJ patients died because of disease progression. Therefore, this table only represents 35 arsa-cel treated and 43 natural history MLD patients.

† Age at arsa-cel administration or age at initial assessment for Natural History participants

Table D3.3. Kaplan-Meier Overall Survival

Trial	Phase I/II, Phase II, Expanded Access Programs[17,18]									
MLD Subtype	Late Infantile				Early Juvenile					
Arm	Pre-symptomatic Arsa-cel		Natural History		Pre-symptomatic Arsa-cel		Early Symptomatic Arsa-cel*		Natural History	
Chronological Age, years	KM %	N at risk	KM %	N at risk	KM %	N at risk	KM %	N at risk	KM %	N at risk
0	100	18	100	27	100	8	100	9	100	21
1	100	18	100	27	100	8	100	9	100	21
2	100	18	100	27	87.5	8	100	9	100	21
3	100	18	100	26	87.5	7	100	9	100	20
4	100	16	96	24	87.5	6	100	9	100	19
5	100	15	92	21	87.5	4	100	8	100	19
6	100	11	62	14	87.5	4	100	8	100	18
7	100	8	49	11	87.5	3	100	7	100	16
8	100	7	49	10	87.5	2	100	7	100	14
9	100	6	49	9	87.5	2	100	7	90	10
10	100	6	49	9	87.5	1	100	7	78	9
11	100	4	38	7	87.5	1	100	7	78	6
12	100	2	23	4	NA		100	7	78	6
13	NA		NA				100	5	78	5
14							100	4	78	5
15							100	3	78	5
16							100	2	78	5
17							100	1	59	4
18							100	1	59	3
19							100	1	59	3

KM %: Kaplan-Meier percent, n: number assessed, N: total number, NA: not applicable, %: percent

* This analysis did not include the two early symptomatic EJ MLD patients who died because of disease progression.

Table D3.4. Gross Motor Function Measure (GMFM) Total Scores: Patients Enrolled Through Phase I/II + Hospital Exemptions + Compassionate Use Programs

Source	Phase I/II Lancet Publication[6]								Orchard Therapeutics* [17]	
MLD Subtype	Late Infantile		Early Juvenile						Early Juvenile	
	Overall		Overall		Pre-symptomatic		Early symptomatic		Early symptomatic	
Arm	Arsa-cel	Natural History	Arsa-cel	Natural History	Arsa-cel	Natural History	Arsa-cel	Natural History	Arsa-cel	Natural History
Year 2										
n Evaluated	11	9	10	11	4	8	6	10	9	13
GMFM Total Score, %	73.1	7.6	78.7	36.7	96.7	44.3	60.7	31.9	86.9	39.6
Treatment Difference, (95%CI); p-value	65.6 (48.9 to 82.3); p<0.0001		42.0 (12.3 to 71.8); p=0.036		52.4 (25.1 to 79.6); p=0.008		28.7 (-14.1 to 71.5); p=0.350		47.2 (22.9 to 72.7); p<0.001	
Year 3										
n Evaluated	10	12	10	12	4	9	6	10	7	10
GMFM Total Score, %	74.3	2.8	72.9	16.3	93.2	18.2	59.8	15.9	74.6	25.5
Treatment Difference, (95%CI); p-value	71.5 (50.3 to 92.7); p=0.0001		56.7 (33.7 to 79.6); p=0.00061		74.9 (50.8 to 99.1); p<0.001		43.9 (9.2 to 78.5); p=0.054		49.1 (17.2 to 81.0); p=0.005	

95%CI: 95 percent confidence interval, GMFM: Gross Motor Function Measure, n: number, N: total number, N/A: not applicable, NR: not reported, p: p-value

* Data comes from Orchard Therapeutics and excludes three patients with symptomatic EJ-MLD who did not fall into revised protocol inclusion criteria.

Note: Not all patients achieved Year 2 assessment due to missed study visit or death.

Table D3.5. Mean Total GMFM-88 Scores: Phase I/II, Phase II, Expanded Access Programs[17,18]

n: number, N: total number, NA: not applicable, NR: not reported, SD: standard deviation

Arms	Late Infantile				Early Juvenile							
	Presymptomatic Arsa-cel (N=18)		Natural History (N=26)		Presymptomatic Arsa-cel (N = 8)		Natural History (N=17)		Early Symptomatic Arsa-cel (N = 9)		Natural History (N=17)	
Timepoint	**n**	**Mean (SD)**	**n**	**Mean (SD)**	**n**	**Mean (SD)**	**n**	**Mean (SD)**	**n**	**Mean (SD)**	**n**	**Mean (SD)**
Baseline	18	47.2 (21.22)	NR	NR	8	72.04 (18.11)	NR	NR	9	92.4 (6.69)	NR	NR
Year 1	17	68.43 (17.18)	NR	NR	5	90.64 (7.9)	NR	NR	9	89.43 (11.9)	NR	NR
Year 2	16	79.34 (10.45)	11	9.08 (9.5)	7	93.52 (5.01)	8	42.58 (32.49)	9	83.25 (18.69)	13	42.15 (33.8)
Year 3	14	84.82 (14.6)	NR	NR	5	97.5 (2.36)	NR	NR	7	72.12 (22.99)	NR	NR
Year 4	12	82.67 (21.32)	NR	NR	3	98.6 (1.24)	NR	NR	5	61.31 (24.82)	NR	NR
Year 5	7	76.66 (28.8)	9	1.9 (1.68)	2	100 (-)	8	23.98 (34.47)	3	46.85 (19.57)	7	12.09 (12.09)
Year 6	6	75.66 (33.48)	NR	NR	2	98.56 (-)	NR	NR	2	67.46 (46.03)	NR	NR
Year 7	6	75.67 (35.73)	NR	NR	1	100 (-)	NR	NR	NR	NR	NR	NR
Year 8	4	85.29 (12.18)	NR	NR	1	98.7 (-)	NR	NR	1	98.89 (-)	NR	NR
Year 9	2	68.94 (-)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Year 10	2	81.74 (-)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Year 11	2	77.95 (-)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR

Table D3.6. Median Total GMFM-88 Scores: Phase I/II, Phase II, Expanded Access Programs[17]

Arm	Late Infantile				Early Juvenile							
	Pre-symptomatic Arsa-cel (N=18)		Natural History (N=26)		Pre-symptomatic Arsa-cel (N=8)		Pre-symptomatic Natural History (N=17)		Early Symptomatic Arsa-cel (N=9)		Early Symptomatic Natural History (N=17)	
Timepoint	**n**	**Median**	**n**	**Median**	**n**	**Median†**	**n**	**Median**	**n**	**Median†**	**n**	**Median**
Baseline	18	51.86	NR	NR	8	69.61	NR	NR	9	87.06	NR	NR
Year 1	17	71.12	NR	NR	5	84.96	NR	NR	9	90.3	NR	NR
Year 2	16	81.55	11	4.8	7	92.71	8	47	9	88.47	13	39.58
Year 3	14	88.81	NR	NR	5	96.56	NR	NR	7	71.21	NR	NR
Year 4	12	91.71	NR	NR	3	98.18	NR	NR	5	62.3	NR	NR
Year 5	7	87.92	9	1.51	2	100	8	8.09	3	48.36	7	2.29
Year 6	6	89.57	NR	NR	2	98.58	NR	NR	2	67.46	NR	NR
Year 7	6	90.13	NR	NR	1	100	NR	NR	1	62.6*	NR	NR
Year 8	4	87.81	NR	NR	1	98.7	NR	NR	1	98.89	NR	NR
Year 9	2	68.94	NR	NR	NA		NR	NR	1	85.57	NR	NR
Year 10	2	81.74	NR	NR			NR	NR	NA		NR	NR
Year 11	2	77.95	NR	NR			NR	NR			NR	NR

CI: confidence interval, n: number, N: total number, NA: not applicable, NR: not reported

* 7.5 years

† Data for single patients are not medians

Table D3.7. ARSA Activity in PBMCs in Arsa-cel Treated Patients

Trial	Phase I/II, Phase II, Expanded Access Programs[17,18]					
Timepoint	Pre-symptomatic Late Infantile (N=18)		Pre-symptomatic Early Juvenile (N=8)		Early Symptomatic Early Juvenile (N=9)	
	n	Median* (nmol/mg/h)	n	Median* (nmol/mg/h)	n	Median (nmol/mg/h)
Baseline	16	25.79	8	25.79	9	25.79
Year 1	18	2028.53	8	771.56	9	169.44
Year 2	16	934.63	7	1242.3	8	88.4
Year 3	15	1557.14	4	1156.09	7	279.82
Year 4	1	1352.5	3	2217.86	4	703.85
Year 5	8	714.29	1	3234.13	3	362.85
Year 6	5	663.29	2	1311.51	2	1264.79
Year 7	6	963.41	1	1835.98	NR	NR
Year 8	4	114.38	1	779.76	NR	NR
Year 9	1	599.2	NR	NR	NR	NR
Year 10	1	328.04	NR	NR	NR	NR
Year 11	2	1357.47	NR	NR	NR	NR

ARSA: arylsulfatase A, n: number, N: total number, nmol/mg/h: nanomole per milligram per hour, NR: not reported, PBMC: peripheral blood mononuclear cells

* Data for single patients are not medians

Table D3.8. Highest Level of Motor Function at Last Follow-up

Trial	Phase I/II, Phase II, Expanded Access Programs[18]				
MLD Subtype	**Late Infantile**		**Early Juvenile**		
Arm	**Pre-symptomatic Arsa-cel**	**Natural History**	**Pre-symptomatic Arsa-cel**	**Early symptomatic Arsa-cel**	**Natural History**
N	18	27*	8	11†	21*
Age range at last GMFC assessment or death (years)	1.6-12.1	2.7-20.4	2.1-11.0	4.6-19.1	2.8-25.3
GMFC 0-2	17	0	7	4	4
GMFC 3-4	0	0	0	3	3
GMFC 5-6	1	8	0	2	11
Deaths	0	19*	1	2	3

GMFC: Gross Motor Function Classification, N: total number

*Natural history cohorts include an additional 5 subjects from study NCT03392987 who are siblings of patients receiving arsa-cel

† Includes the two patients who died from disease progression.

Table D3.9. Time From Birth to Confirmed Loss of Independent Ambulation

Trial	Phase I/II, Phase II, Expanded Access Programs [17,18]									
MLD Subtype	Late Infantile				Early Juvenile					
Arm	Pre-symptomatic Arsa-cel		Natural History		Pre-symptomatic Arsa-cel		Early Symptomatic Arsa-cel		Natural History	
Chronological Age, Years	Kaplan-Meier Percent	n	Kaplan-Meier Percent	n	Kaplan-Meier Percent	n	Kaplan-Meier Percent	n	Kaplan-Meier Percent	n
0	100	18	100	26	100	8	100	9	100	17
1	100	18	100	26	100	8	100	9	100	17
2	83	14	50	13	100	8	100	9	100	16
3	83	14	4	1	100	7	100	9	93	15
4	76	11	0	0	100	6	100	9	87	14
5	76	11	0	0	100	4	100	8	68	11
6	76	7	0	0	100	4	100	8	27	4
7	76	4	0	0	100	3	85	6	13	2
8	56	3	0	0	100	2	71	5	7	1
9	56	3	0	0	100	2	42	3	7	1
10	56	3	0	0	100	1	42	3	0	0
11	56	2	0	0	100	1	42	3	0	0
12	0	0	0	0	0	0	30	2	0	0
13	NA		NA		NA		30	2	0	0
14							30	1	0	0
15							30	1	0	0
16							0	0	0	0

N: number, NA: not applicable

Table D3.10. Time From Birth to Loss of Walking Ability

Trial	Phase I/II, Phase II, Expanded Access Programs [17,18]									
Arm	Late Infantile				Early Juvenile					
	Pre-symptomatic Arsa-cel		Natural History		Pre-symptomatic Arsa-cel		Early Symptomatic Arsa-cel		Natural History	
Chronological Age, years	Kaplan-Meier Percent	n	Kaplan-Meier Percent	n	Kaplan-Meier Percent	n	Kaplan-Meier Percent	n	Kaplan-Meier Percent	n
0	100	18	100	26	100	8	100	9	100	17
1	100	18	100	26	100	8	100	9	100	17
2	100	17	88	23	100	8	100	9	100	16
3	100	17	15	4	87	7	100	9	93	15
4	100	15	4	1	87	6	100	9	93	15
5	94	14	0	0	87	4	100	8	86	13
6	94	9	0	0	87	4	100	8	50	7
7	94	6	0	0	87	3	100	7	36	4
8	94	5	0	0	87	2	100	7	27	3
9	94	5	0	0	87	2	100	7	9	1
10	94	5	0	0	87	1	72	5	0	0
11	94	3	0	0	87	1	43	3	0	0
12	94	1	0	0	0	0	43	3	0	0
13	0	0	0	0	NA		43	3	0	0
14	NA		NA				43	2	0	0
15							43	2	0	0
16							21	1	0	0
17							0	0	0	0

N: number, NA: not applicable

Table D3.11. Time From Birth to GMFC Level >5 or Death (Severe Motor Impairment Free Survival)

Trial	Phase I/II, Phase II, Expanded Access Programs [18]									
Arm	Late Infantile				Early Juvenile					
	Pre-symptomatic Arsa-cel		Natural History		Pre-symptomatic Arsa-cel		Early Symptomatic Arsa-cel		Natural History	
Chronological Age, years	Kaplan-Meier percent	n	Kaplan-Meier percent	n	Kaplan-Meier percent	n	Kaplan-Meier percent	n	Kaplan-Meier percent	n
0	100	18	100	27	100	8	100	11	100	21
1	100	18	100	27	100	8	100	11	100	21
2	100	17	96	26	88	8	100	11	100	20
3	100	17	22	6	88	7	100	11	100	19
4	100	15	7	2	88	6	100	11	100	19
5	100	15	0	0	88	4	100	10	100	17
6	100	10	0	0	88	4	100	10	72	12
7	100	7	0	0	88	3	100	7	45	6
8	83	5	0	0	88	2	100	7	30	4
9	83	5	0	0	88	2	100	7	11	1
10	83	5	0	0	88	1	100	7	11	1
11	83	3	0	0	88	1	100	7	0	0
12	83	1	0	0	0	0	100	7	0	0
13	0	0	0	0	NA		86	5	0	0
14	NA		NA				86	4	0	0
15							86	3	0	0
16							58	2	0	0
17							58	1	0	0
18							58	1	0	0
19							58	1	0	0
20							0	0	0	0

N: number, NA: not applicable

Table D3.12. Performance Standard Score/Development Quotient Performance Data by GMFC-MLD Level: Early Juvenile MLD

Trial	Phase I/II, Phase II, Expanded Access Programs[17]					
Arm	Pre-symptomatic EJ Arsa-cel (N=8)		Early Symptomatic EJ Arsa-cel (N=9)		EJ Natural History (N=17)	
GMFC-MLD Level	n*	Mean (SD)	n*	Mean (SD)	n*	Mean (SD)
GMFC-MLD 0	51	111.9 (18.75)	28	108.1 (16.39)	0	NR
GMFC-MLD 1	6	NR	13	98.6 (10.52)	5	54.8 (24.09)
GMFC-MLD 2	4	NR	16	104.8 (32.76)	12	26.3 (23.13)
GMFC-MLD 3	4	NR	4	98.0 (55.82)	0	NR
GMFC-MLD 4	2	NR	7	106.9 (10.81)	4	30.5 (28.30)
GMFC-MLD 5	2	NR	1	89.0 (NC)	21	2.0 (1.02)
GMFC-MLD 6	0	NR	0	NR	26	0.8 (0.61)

EJ: early juvenile, GMFC: Gross Motor Function Classification, n: number, NC: not calculable, NR: not reported, SD: standard deviation

*n = the number of patient visits contributing to the mean

Table D3.13. Nerve Conduction Velocity and Brain Imaging Outcomes

Trial			Phase I/II, EAFs and CUPs [6]			
Subtype			Late Infantile		Early Juvenile	
Arm			Arsa-cel	Natural History	Arsa-cel	Natural History
Total N			16	19	13	12
Nerve Conduction Velocity (NCV)	Year 2	n Evaluated	9	10	NR	NR
		Mean NCV Index	-7.6	-13.3	NR	NR
		Treatment Difference, (95%CI); p-value	5.8 (2.4-9.1); p=0.004		NR	
	Year 3	n Evaluated	6	8	NR	NR
		Mean NCV Index	-8.3	-11.5	NR	NR
		Treatment Difference, (95%CI); p-value	3.2 (1.0-5.3); p=0.010		NR	
Total MRI Severity Score	Year 2	n Evaluated	9	15	10	11
		Mean Total MRI Severity Scores	2.4	15.3	9.4	17.9
		Treatment Difference, (95%CI); p-value	12.9 (9.7-16.2); p<0.001		8.5 (2.3-14.7); p=0.010	
	Year 3	n Evaluated	8	9	9	12
		Mean Total MRI Severity Scores	3.6	21.7	10.1	20.5

		Treatment Difference, (95%CI); p-value	18.1 (15.0-21.1); p<0.001	10.4 (3.8-17.0); p=0.004

95% CI: 95 percent confidence interval, ES: early symptomatic, MRI: magnetic resonance imaging, n: number, N: total number, NCV: nerve conduction velocity, NR: not reported, p: p-value, PS: pre-symptomatic

Table D3.14. Safety

Phase of Treatment with Arsa-cel		Busulfan Conditioning Phase	3 Months Post-Gene Therapy[17]	7.5 Years Follow-Up Post-Gene Therapy[6]
N		**39**	**39**	**29**
Adverse Events, n (%)	Overall	NR	NR	29 (100)
	Grade 3/4	12 (31)	37 (98)	29 (100)
Treatment-related Adverse Events, n (%)	Overall	NR	NR	6 (15.38)*
	Serious	NR	NR	0
Death, n (%)	Overall	NR	NR	3 (7.69)*
	Adverse Event-related	NR	NR	1 (3.4)
	Treatment-related	NR	NR	0
Busulfan-related Adverse Events (Grade ≥3), n (%)	Febrile Neutropenia	NR	32 (82)	23 (79)
	Stomatitis	NR	29 (74)	12 (41)
	Mucositis/Mucosal Inflammation	NR	NR	9 (31)
	Neutropenia	NR	8 (21)	5 (17)
	Infections	5 (13)†	NR	5 (17)†
	Vomiting	NR	3 (8)	4 (14)
	Enteritis	NR	NR	3 (10)
	Metabolic Acidosis	NR	2 (5)	3 (10)
	Pneumonia	NR	NR	3 (10)
	Veno-occlusive Disease	NR	2 (5)	3 (10)
	Atypical Hemolytic Uremic Syndrome	NR	NR	2 (7)
	Clostridium Difficile Colitis	NR	2 (5)	2 (7)
	Epistaxis	NR	NR	2 (7)
	Rash Erythematous	NR	3 (8)	2 (7)
Post-gene Therapy Adverse Events Related to MLD progression (Grade ≥3), n (%)	Gait Disturbance	NR	5 (15)	15 (52)
	Motor Dysfunction	NR	2 (5)	9 (31)
	Muscle Spasticity	NR	NR	9 (31)
	Aphasia	NR	NR	6 (21)
	Ataxia	NR	2 (5)	5 (17)

	Seizures	NR	NR	2 (7)
	Cognitive Disorder	NR	NR	4 (14)
	Dysarthria	NR	NR	5 (17)
	Dysphagia	NR	NR	4 (14)
Gene Therapy-related Late Harms, n (%)	Anti-ARSA Antibodies	NR	NR	6 (15.38)*
	Malignancies	NR	NR	0
	Insertional Oncogenesis	NR	NR	0
	Bone Marrow Abnormalities	NR	NR	NR

ARSA: arylsulfatase A, MLD: metachromatic leukodystrophy, n: number, N: total number, NR: not reported

* 7.5 year data replaced with updated safety from Phase I/II, Phase II, and Expanded Access Program population (N=39) from up to 11 years of follow-up where available

† Device-related infection

D4. Ongoing Studies

Table D4.1. Ongoing Studies

Title & Trial Sponsor	Study Design & Treatment Arm	Patient Population	Primary Outcomes	Estimated Completion
OTL-200 in Patients With Late Juvenile Metachromatic Leukodystrophy (MLD)* Orchard Therapeutics NCT04283227	Phase III, Single group intervention, Open-Label, Non-randomized Trial **Estimated enrollment:** N=6 **Treatment Arm**: Intravenous (IV) infusion of OTL-200 gene therapy following conditioning regimen with busulfan	**Inclusions**: - Documented biochemical and molecular diagnosis of MLD, based on ARSA activity below the normal range and identification of two disease-causing ARSA alleles. - 0/R or R/R genotype or a genotype recognized as associated with the late juvenile variant of MLD. - If pre-symptomatic: • Participant must be <17 years of age at treatment AND must have a sibling with a diagnosis of late-juvenile MLD variant based on age at disease with biochemical and molecular diagnosis. Normal cognitive function as defined by an IQ≥85 on age-appropriate cognitive scales. - If the participant is <7 years: • Normal motor milestones achievement, normal gross motor function according to chronological age and normal neurological examination - If participant is ≥7 years: • Normal gross motor function or mild gross motor function impairment, defined by a GMFC-MLD 0 or 1 **Exclusions**: - Has previously undergone allogeneic HSPC gene therapy (HSPC-GT) and has evidence of residual cells of donor origin.	- Change from baseline in ARSA activity levels in Cerebrospinal Fluid [at 24 months] - Change from baseline in neuronal metabolite ratio of N-acetyl-aspartate (NAA) to creatine (Cr) in white matter regions of the brain [at 24 months]	03/31/2031

Source: www.ClinicalTrials.gov

* This trial population is patients with late juvenile MLD, a population not in the scope of this current review.

GMFC: Gross Motor Function Classification, GT: gene therapy, HSPC: hemopoietic stem cell transplantation, IQ: intelligence quotient, MLD: metachromatic leukodystrophy, N: total number

D5. Previous Systematic Reviews and Technology Assessments

We identified two health technology assessments (HTA) of arsa-cel for the treatment of MLD previously conducted by the National Institute for Health and Care Excellence (NICE), and the HTA collaboration network of Fimea (Finland), NoMA (Norway) and TLV (Sweden) (FINOSE). We also identified one systematic literature review comparing arsa-cel to standard of care and hemopoietic stem cell transplantation. All assessments are summarized below.

NICE Technology Assessment[23]

NICE conducted a health technology assessment to evaluate the safety and efficacy of arsa-cel for the treatment of MLD. The organization considered evidence submitted by Orchard Therapeutics, which consisted of a clinical program involving 35 patients with up to eight years of follow-up across two clinical studies and three Expanded Access Programs. Due to ethical and practical reasons, none of the studies had a control arm and instead used data from an age and disease subtype-matched study as the comparator group. The evaluation committee deemed the efficacy and safety data to show that arsa-cel provides meaningful clinical benefits in the treatment of pre-symptomatic LI-MLD, pre-symptomatic EJ-MLD, and early symptomatic EJ-MLD patients. Arsa-cel showed evidence of preserving cognitive function, delaying time to severe motor disability, and slowing down brain demyelination and atrophy. The committee concluded that the safety findings in subjects treated with arsa-cel were in line with what would be expected in subjects who have undergone busulfan conditioning and hematological reconstitution. Based on these reasons, the committee believed offering a positive recommendation of arsa-cel would significantly contribute to MLD patients, their caregivers, and families.

FINOSE Technology Assessment[22]

In a health technology assessment, FINOSE compared arsa-cel to best supportive care to evaluate its effectiveness in treating MLD. FINOSE assessed efficacy in a population constructed using participants from a single-arm Phase I/II clinical trial and three expanded access programs, based on submitted data from Orchard Therapeutics. FINOSE evaluated the data on two primary endpoints: improvement of GMFM score compared to the untreated population, and increase in the ARSA activity compared to the baseline at two years after treatment. The GMFM score exceeded the pre-defined improvement threshold by 10% in all patient groups. The ARSA activity in PBMC increased at levels higher than reported for healthy subjects, and at two years post-treatment there was a statistically significant increase in ARSA activity for both LI-MLD and EJ-MLD subgroups compared to baseline. However, whether the co-primary endpoint related to ARSA activity was met was uncertain because no correlation between the ARSA activity and other clinical outcomes was observed. Based on the results of their analysis, FINOSE deemed it clear that the treated patients mostly stay alive and do not develop severe symptoms of MLD that are seen in the natural course of the disease. However, FINOSE found an uncertainty regarding Orchard Therapeutics' assumption

on the comparability of the treated and untreated populations, as disease progression seemed slower in the treated population already before the treatment started. Another uncertainty, due to the short follow-up time, was that the risk of long-term adverse events had yet to be evaluated, and that common adverse events might be missed because of the very limited number of treated subjects. Along with granting market authorization for arsa-cel, FINOSE requested that Orchard Therapeutics use a registry of patients to learn more about the long-term efficacy and safety of the medicine.

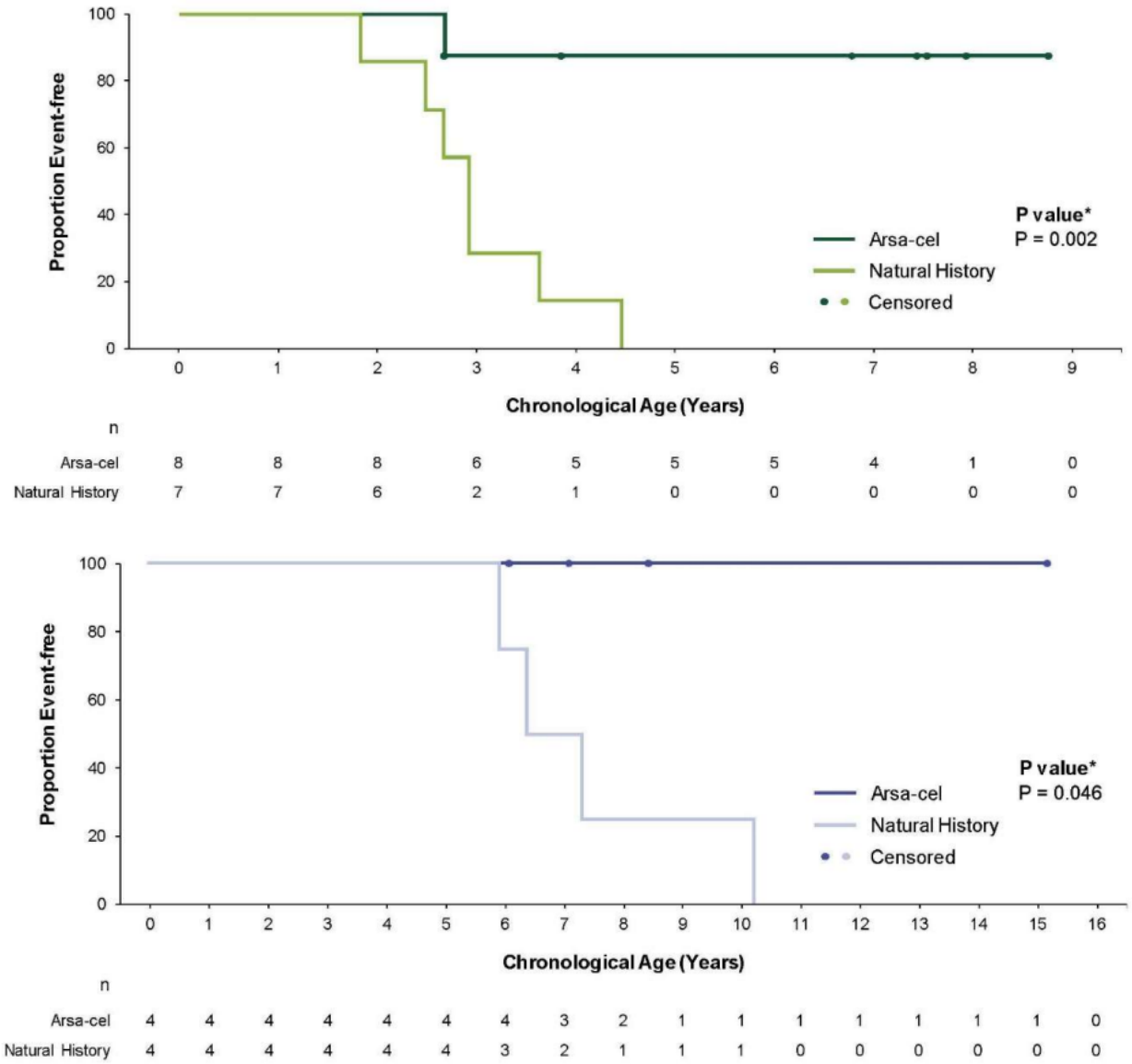
Armstrong N, Olaye A, Noake C, et al. A systematic review of clinical effectiveness and safety for historical and current treatment options for metachromatic leukodystrophy in children, including atidarsagene autotemcel. Orphanet Journal of Rare Diseases. 2023 Aug; 18(1):248.

This systematic review compared the efficacy and safety of arsa-cel in comparison to standard of care and allogeneic hematopoietic stem cell transplantation (HSCT). References relating to 12 studies, mostly single-arm studies, were included with one study comparing arsa-cel to a natural history population and two studies comparing HSCT to standard of care. Trials were compared across various key efficacy outcomes such as survival, disease progression, gross motor function, neurological and cognitive function, and safety, when data allowed. Treatment with arsa-cel improved children's prognosis of survival significantly in those with late-infantile MLD (100% survival of all children with LI-MLD at latest follow-up as compared to 50-60% and 19% survival in children treated with HSCT or standard of care alone respectively after five to six years of follow-up. Survival in children with early-juvenile MLD was similar across the three treatment groups. A substantial percentage of patients treated with HSCT showed disease progression, including motor and cognitive decline. This was in contrast to those treated with arsa-cel, many of whom retained motor function and had normal acquisition of cognitive skills. Finally, there was a risk of treatment associated death with HSCT; such risk was not seen in the arsa-cel studies. Overall, the review found that treatment with arsa-cel as compared to standard of care and HSCT results in markedly improved survival and motor and cognitive function for children with MLD.

D6. Heterogeneity and Subgroups

Data from the exploratory matched sibling analysis showed a similar pattern of severe motor-impairment free survival or death as the main analysis for both the LI and EJ-MLD subgroups (Figure D6.1).[6] In both groups, arsa-cel treated patients had statistically significant greater survival than their sibling counterparts in the natural history group. Additionally, treated patients showed continued acquisition of cognitive skills as expected for their age as compared with their siblings.

Figure D6.1. Severe Motor-Free Impairment Survival or Death in Matched Sibling Analysis for Late-Infantile (top panel) and Early Juvenile (bottom panel) Subgroups [6]



E. Long-Term Cost-Effectiveness: Supplemental Information

E1. Detailed Methods

Table E1.1. Impact Inventory

Sector	Type of Impact (Add additional domains, as relevant)	Included in This Analysis from […] Perspective?		Notes on Sources (if quantified), Likely Magnitude & Impact (if not)
		Health Care Sector	Societal	
Formal Health Care Sector				
Health Outcomes	Longevity effects	X	X	
	Health-related quality of life effects	X	X	
	Adverse events	X	X	
Medical Costs	Paid by third-party payers	X	X	
	Paid by patients out-of-pocket	☐	☐	
	Future related medical costs	X	X	
	Future unrelated medical costs	☐	☐	
Informal Health Care Sector				
Health-Related Costs	Patient time costs	NA	☐	
	Unpaid caregiver-time costs	NA	☐	
	Transportation costs	NA	☐	
Non-Health Care Sector				
Productivity	Labor market earnings lost	NA	X	For caregivers
	Cost of unpaid lost productivity due to illness	NA	X	For caregivers
	Cost of uncompensated household production	NA	☐	
Consumption	Future consumption unrelated to health	NA	☐	
Social Services	Cost of social services as part of intervention	NA	☐	
Legal/Criminal Justice	Number of crimes related to intervention	NA	☐	
	Cost of crimes related to intervention	NA	☐	
Education	Impact of intervention on educational achievement of population	NA	☐	
Housing	Cost of home improvements, remediation	NA	☐	
Environment	Production of toxic waste pollution by intervention	NA	☐	
Other	Other impacts (if relevant)	NA	☐	

NA: not applicable

Adapted from Sanders et al[60]

Description of evLY Calculations

The equal value life year (evLY) considers any extension of life at the same "weight" no matter what treatment is being evaluated or what population is being modeled. Below are the stepwise calculations used to calculate the evLY.

1. First, we attribute a utility of 0.851, the age- and sex-adjusted utility of the general population in the US that are considered healthy.[26]
2. We calculate the evLY for each model cycle.
3. Within a model cycle, if using the intervention results in additional life years versus the primary comparator, we multiply the general population utility of 0.851 with the additional life years gained (ΔLY gained) within the cycle.
4. The life years shared between the intervention and the comparator use the conventional utility estimate for those life years within the cycle.
5. The total evLY for a cycle is calculated by summing steps 3 and 4.
6. The evLY for the comparator arm is equivalent to the QALY for each model cycle.
7. The total evLYs are then calculated as the sum of evLYs across all model cycles over the time horizon.

Finally, the evLYs gained is the incremental difference in evLYs between the intervention and the comparator arm.

Target Population

The population of focus for the economic evaluation included presymptomatic LI-MLD, presymptomatic EJ-MLD, and early symptomatic EJ-MLD patients. The usual care arm in the model was informed from natural history data.[2,61,62] The baseline characteristics of arsa-cel subtypes from the clinical trials were provided by the manufacturer and were used to inform the model population (Table E1.2).

Table E1.2. Trial Baseline Population Characteristics

	Arsa-cel		
	Presymptomatic LI (n=18)	**Presymptomatic EJ (n=8)**	**Early Symptomatic EJ (n=9)**
Mean Age at Gene Therapy/First Contact	18 months	24 months	73 months
Female, n (%)	5 (27.78)	2 (25.00)	3 (33.33)

EJ: early juvenile, LI: late infantile

E2. Model Inputs and Assumptions

Model Inputs

Clinical Inputs

Mean time to each health state for the usual care arm based on natural history was used to inform transition probabilities (Table E2.1). Monthly transition probabilities before stabilization for stable partial responders were provided by the manufacturer to align with clinical trial results (Table E2.2). Progression modifiers (Table E2.3) were used to inform transition probabilities for unstable partial responders. Progression modifiers were also used to inform transition probabilities for full responders and stable partial responders after the stabilization period ended.

Table E2.1. Mean Time (Months) to Each Health State

GMFC-MLD Transition	LI MLD	EJ MLD
From GMFC-MLD 0 to 1	3.3	9.4
From GMFC-MLD 1 to 2	3.7	14.5
From GMFC-MLD 2 to 3	3.7	3.7
From GMFC-MLD 3 to 4	3.7	3.7
From GMFC-MLD 4 to 5	3.7	3.7
From GMFC-MLD 5 to 6	9.6	27.7
From GMFC-MLD 6 to death	57.3	57.6

GMFC-MLD: gross motor function classification – metachromatic leukodystrophy, LI: late infantile, EJ: early juvenile

Table E2.2. Monthly Transition Probabilities Before Stabilization in Stable Partial Responders

GMFC-MLD Transition	LI MLD	EJ MLD
Staying in GMFC-MLD 0	36.79%	36.79%
Staying in GMFC-MLD 1	95.75%	97.33%
Staying in GMFC-MLD 2	99.00%	36.79%
Staying in GMFC-MLD 3	71.65%	99.34%
Staying in GMFC-MLD 4	71.65%	79.67%
Staying in GMFC-MLD 5	90.11%	96.45%
Staying in GMFC-MLD 6	98.27%	98.25%

GMFC-MLD: gross motor function classification – metachromatic leukodystrophy, LI: late infantile, EJ: early juvenile

Table E2.3. Progression Modifiers for Unstable Partial Responders

GMFC-MLD Transition	LI MLD	EJ MLD
Staying in GMFC-MLD 0	1.0	1.0
Staying in GMFC-MLD 1	11.3	1.2
Staying in GMFC-MLD 2	6.4	6.4
Staying in GMFC-MLD 3	6.4	6.4
Staying in GMFC-MLD 4	6.4	6.4
Staying in GMFC-MLD 5	1.0	1.0
Staying in GMFC-MLD 6	1.0	1.0

GMFC-MLD: gross motor function classification – metachromatic leukodystrophy, LI: late infantile, EJ: early juvenile

Utilities

The rescaled set of utilities that does not allow for negative values are presented in Table E2.4. Rescaled utilities were as a scenario analysis because it is difficult to assess values lower than 0, which is a health state valued as "worse than death" meaning patients would rather be dead than be in the health state. There were face validity concerns that as early as GMFC-MLD 3, where patients were still sitting without support, crawling, and rolling, participants rated this health state below 0. An additional source of uncertainty related to the use of proxy respondents, i.e. adult respondents valuing health states for children with MLD. As a result, we used an alternative, rescaled set of utility values where negative utility values were not possible as a scenario analysis. Specifically, for presymptomatic and early symptomatic EJ-MLD, we used the distributions shown in Supplement Table E2.5 (usual care) and Supplement Table E2.6 (arsa-cel) to apply the cognitive-specific utility values.[22] We note that the original rescaled values had a logical inconsistency. We therefore corrected this inconsistency assuming that worse cognitive impairment levels could not have a higher utility value versus better levels.

Table E2.4. Rescaled Health State Utilities

Health State	Late Infantile	Early Juvenile		
		Normal Cognitive Function	Moderate Cognitive Impairment	Severe Cognitive Impairment
GMFC 0	Age adjusted general population		0.75	0.46
GMFC 1	0.71	0.91	0.63	0.34
GMFC 2	0.44	0.84	0.56	0.27
GMFC 3	0.13	0.38	0.10	0.08
GMFC 4	0.04	0.17	0.01	0.01*
GMFC 5	0.01	0.07	0.00	0.00†
GMFC 6	0.00	0.03	0.00	0.00

GMFC-MLD: Gross Motor Function Classification in MLD

* Corrected from 0.03

†Corrected from 0.01

Health state utilities in the early juvenile subtypes were further categorized based on cognitive sub-state distributions for both natural history (Table E2.4) and arsa-cel (Table E2.5).

Table E2.5. Cognitive Sub-State Distribution by GMFC-MLD State in Early Juvenile Natural History

Cognitive Sub-State Distribution	Normal/Mild Cognitive Function	Moderately Cognitive Impairment	Severe Cognitive Impairment
GMFC-MLD 0	100%	0%	0%
GMFC-MLD 1	54%	38%	9%
GMFC-MLD 2	33%	43%	25%
GMFC-MLD 3	25%	35%	40%
GMFC-MLD 4	16%	28%	55%
GMFC-MLD 5	8%	21%	71%
GMFC-MLD 6	0%	14%	86%

GMFC-MLD: Gross Motor Function Classification in MLD

Table E2.6. Cognitive Sub-State Distribution by GMFC-MLD State in Early Juvenile Arsa-cel

Cognitive Sub-State Distribution	Normal/Mild Cognitive Function	Moderately Cognitive Impairment	Severe Cognitive Impairment
GMFC-MLD 0	100%	0%	0%
GMFC-MLD 1	95%	5%	0%
GMFC-MLD 2	95%	5%	0%
GMFC-MLD 3	90%	5%	5%
GMFC-MLD 4	80%	10%	10%
GMFC-MLD 5	80%	10%	10%
GMFC-MLD 6	80%	10%	10%

GMFC-MLD: Gross Motor Function Classification in MLD

To estimate disutility, caregivers (n=21) completed the EuroQol-5 Dimension (EQ-5D-5L) and the mean index utility value was calculated to be 0.773.[29] This was then subtracted from the US general population utility at 40 years of age (0.841), resulting in a disutility of -0.068. The model assumes an average of one caregiver per patient. This disutility was applied from the GMFC-MLD 2 health state onward (Supplement Table E2.7).

Table E2.7. Alternate Set of Caregiver Disutilities

MLD	
Health state	**Disutility**
GMFC-MLD 0	0
GMFC-MLD 1	0
GMFC-MLD 2	-0.068
GMFC-MLD 3	-0.068
GMFC-MLD 4	-0.068
GMFC-MLD 5	-0.068
GMFC-MLD 6	-0.068

GMFC-MLD: Gross Motor Function Classification in MLD

Administration and Monitoring Costs

Table E2.8. describes the administrative procedures, the time taken to perform these procedures, and the cost associated with them. Of note, the follow-up transplant costs refer to follow-up costs pediatric patients following autologous HSCT in the 100 days after receiving a myeloablative conditioning regimen.[63]

Table E2.8. Procedural and Associated Costs of Arsa-cel Treatment

Item	Unit Value	Quantity	Total Cost	Notes and Source
Leukapheresis (Cell Harvest)	$83	1	$83	CPT code 38206 to report harvesting of autologous peripheral stem cells. Source: CMS Physician Fee Schedule
Hospitalization (Conditioning)	$3,556	5.4 (days)	$19,203	HCUP NIS estimates for CCSR: END016, includes ICD-10 E7525 for MLD
Busulfan (Conditioning)	$775	1	$775	NDC: 67457-0893-08 Busulfan 60 mg/10 mL
Autologous Bone Marrow Transplant with Complication	$2,427	18.3 (days)	$44,421	DRG 016 [64]
Autologous Bone Marrow Transplant without Complication	$2,760	11.6 (days)	$32,020	DRG 017[64]
Follow-up Autologous Transplant Costs	$116,646		$116,646	Autologous pediatric patients calculated by subtracting the median Index hospitalization cost from the median total 100-day cost to estimate the non-index 100-day hospitalization cost (assumed to be the follow-on costs).

CPT: Current Procedural Terminology, DRG: diagnosis-related group, mg: milligram, ml: milliliter, NDC: National Drug Code, HCUP NIS: Healthcare Cost and Utilization Project National Inpatient Sample

Adverse Event Costs

Patients receiving arsa-cel experienced grade 3 AEs or higher as noted in Table E2.9. AEs were broken down by the timing of the adverse event (pre-treatment, treatment phase, post-treatment). For patients who experienced a pre-treatment or post-treatment adverse event, the associated costs were assumed to be absorbed by the hospitalization costs for conditioning and follow-up autologous treatment costs, respectively, as specified in Table E2.8. To estimate the AE costs for patients who experience an AE during the treatment phase (26%), the autologous bone marrow transplant costs with complication versus without complication were weighted by 26% versus 74%, respectively.

Table E2.9. Grade 3 Adverse Events Experienced with Arsa-cel

Timing of Adverse Event	Grade 3 or Higher	Cost and Rationale
Pre-Treatment	N=12 (31%)	AE costs will be absorbed by hospitalization costs for conditioning
Treatment Phase	N=10 (26%)	Autologous bone marrow transplant costs with complication vs. without complication will be weighted 26% vs. 74%
Post-Treatment	N=37 (95%)	AE costs will be absorbed by follow-up post-transplant costs

AE: adverse event, N: number

E3. Results

To illustrate the percentage of patients by health state as they progress through the lifetime model, we present the figures by treatment arm and subtype in Figures E3.1 through E3.6.

Figure E3.1. Disease Progression for Usual Care, Presymptomatic LI-MLD

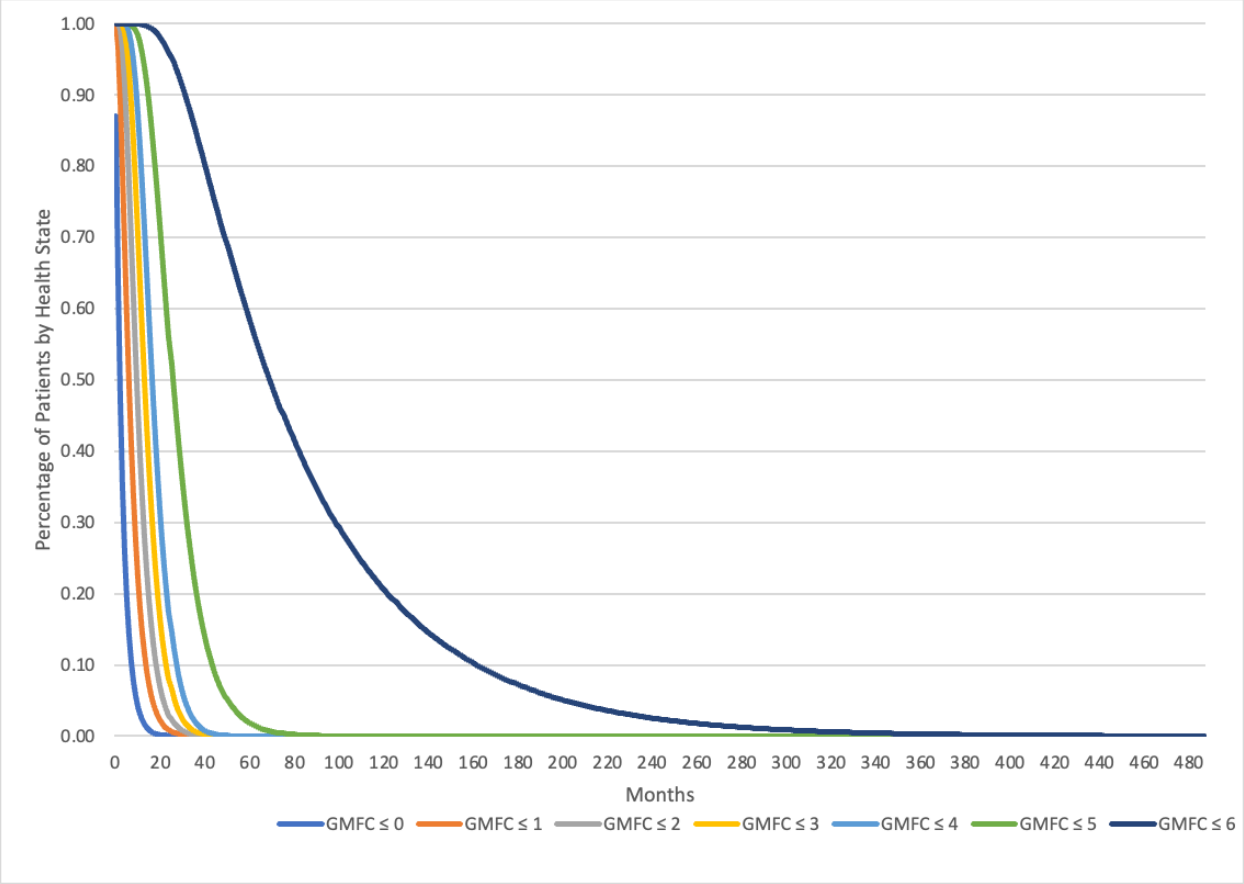


Figure E3.2 Disease Progression for Usual Care, Presymptomatic EJ-MLD

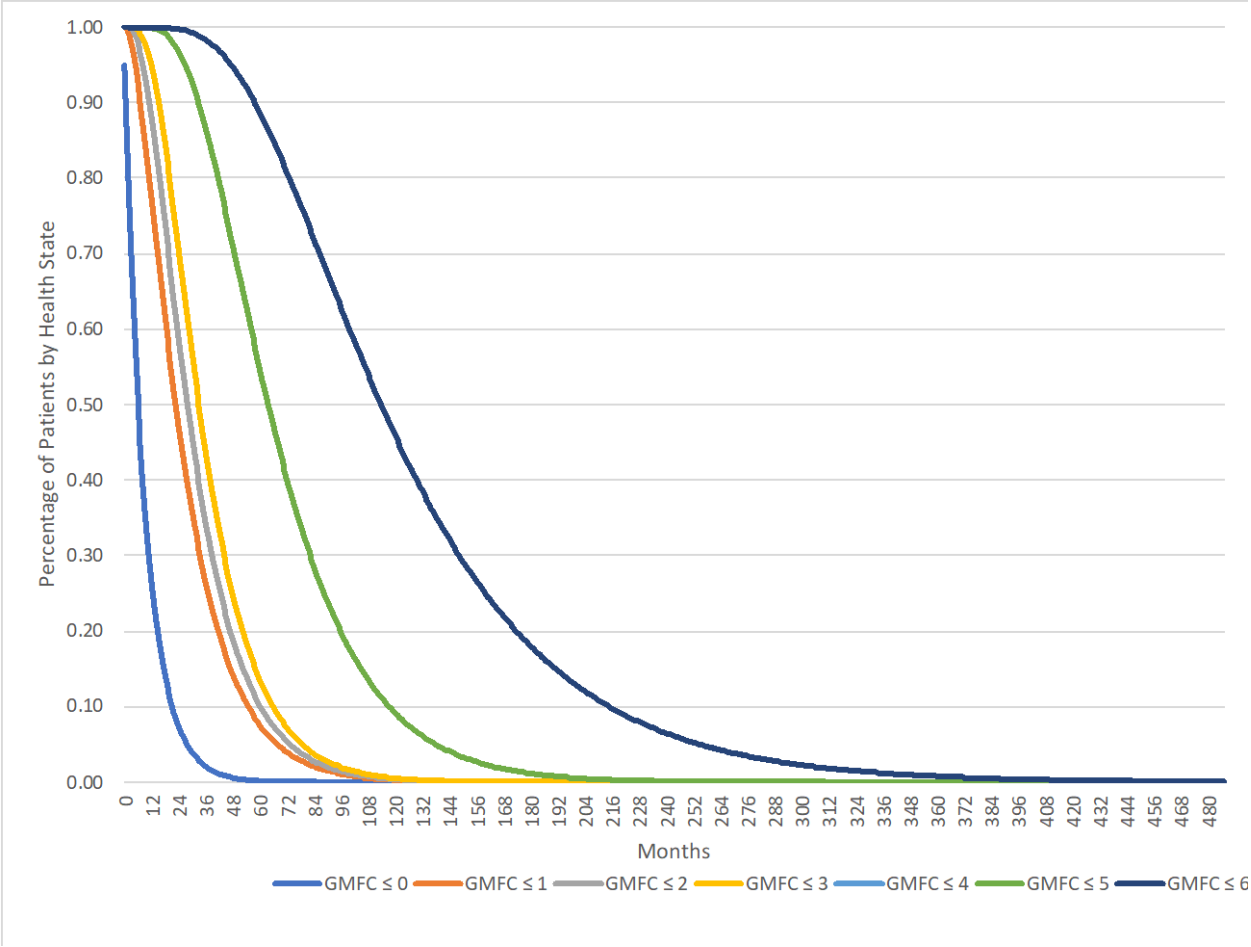


Figure E3.3 Disease Progression for Usual Care, Early Symptomatic EJ-MLD

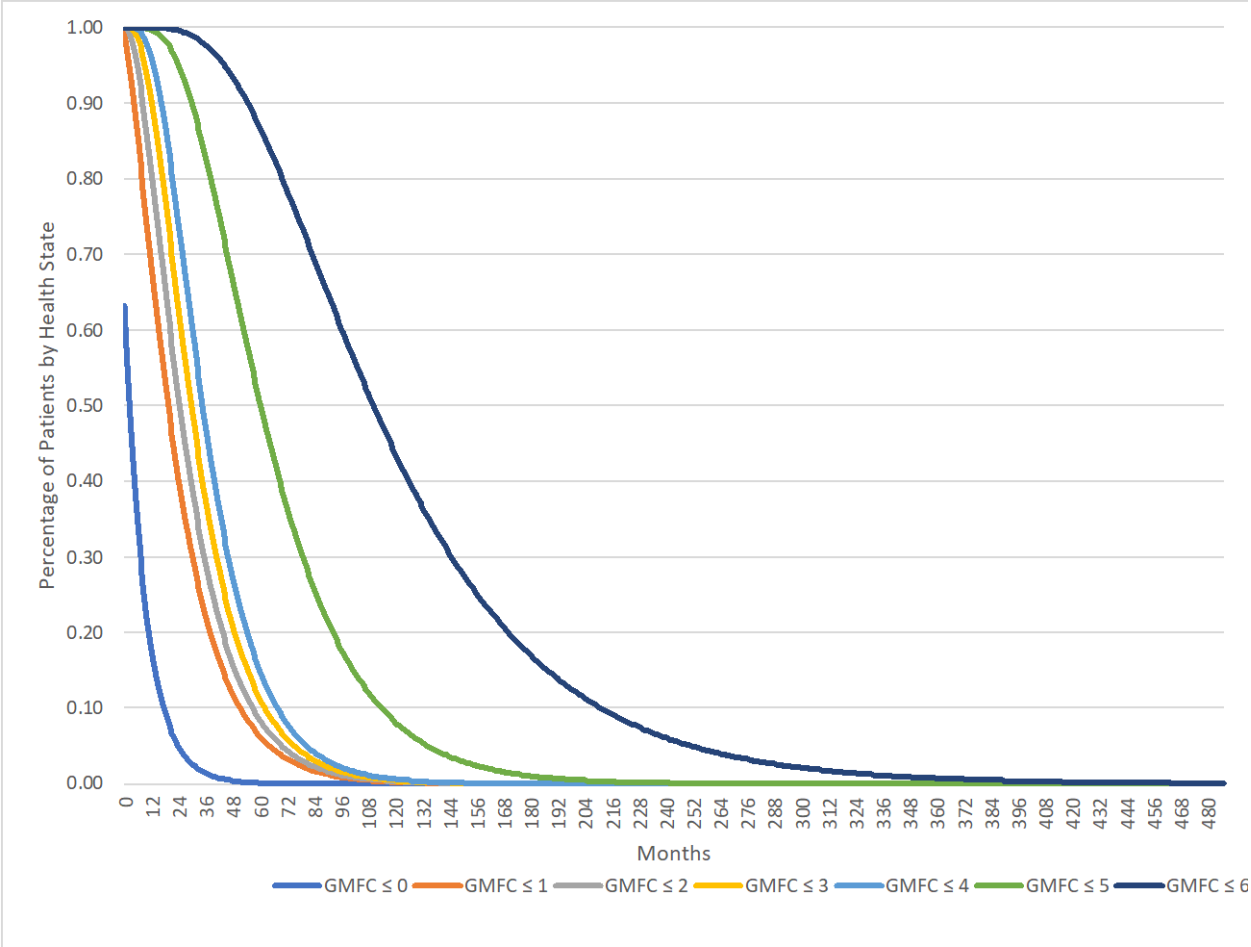


Figure E3.4 Disease Progression for arsa-cel, Presymptomatic LI-MLD

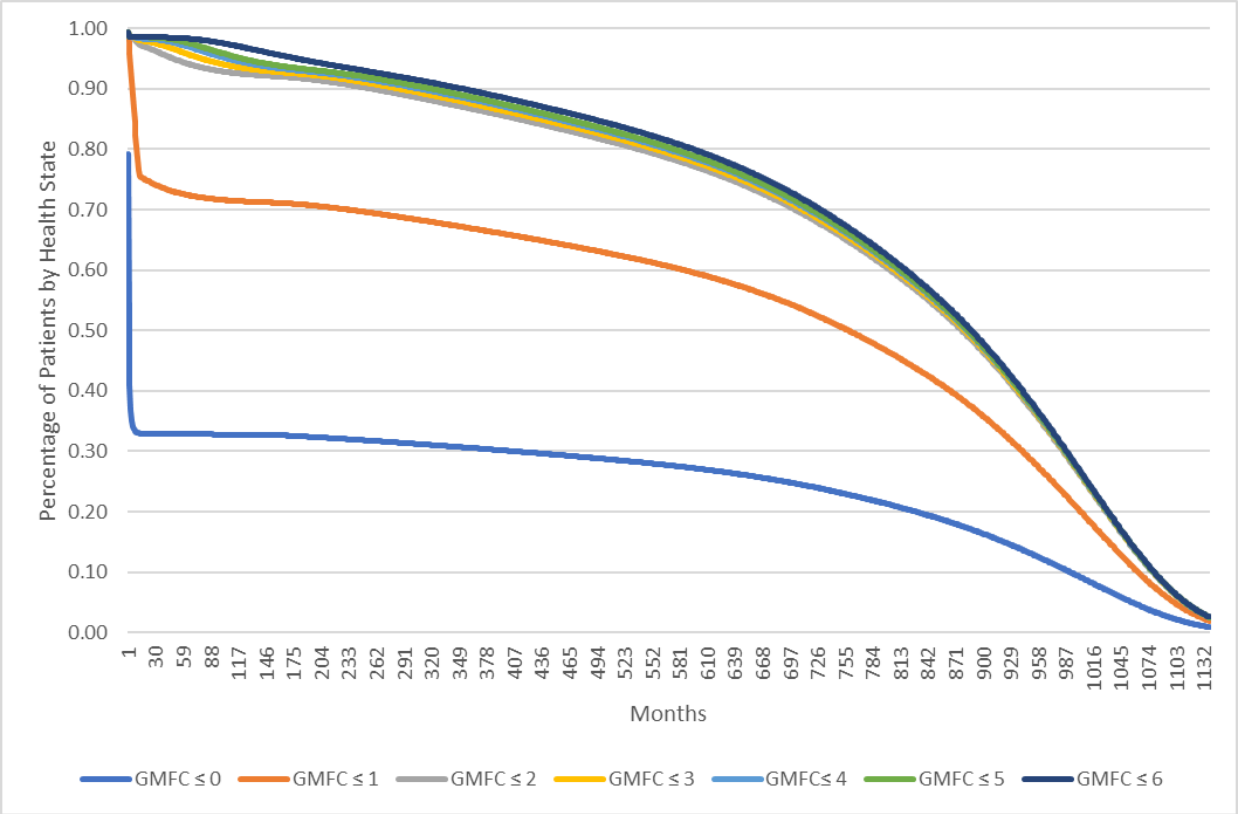


Figure E3.5 Disease Progression for arsa-cel, Presymptomatic EJ-MLD

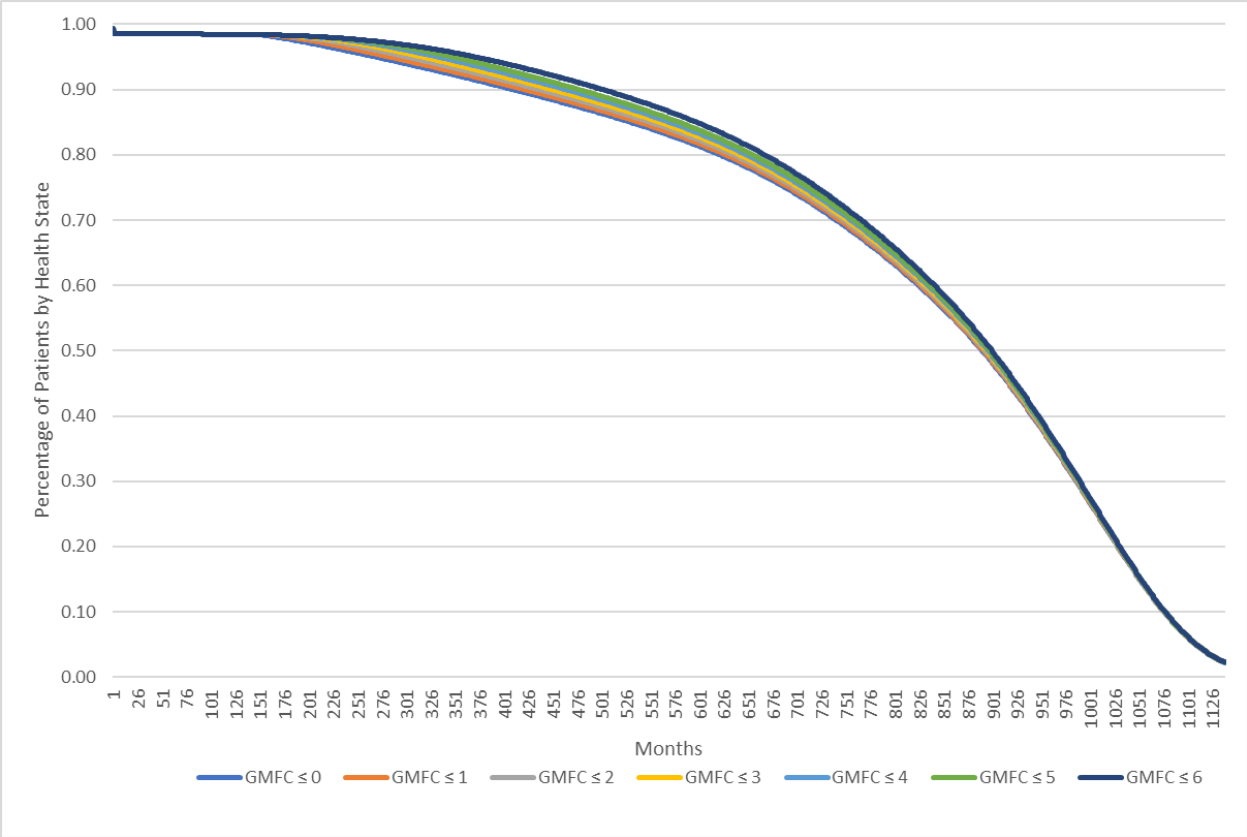
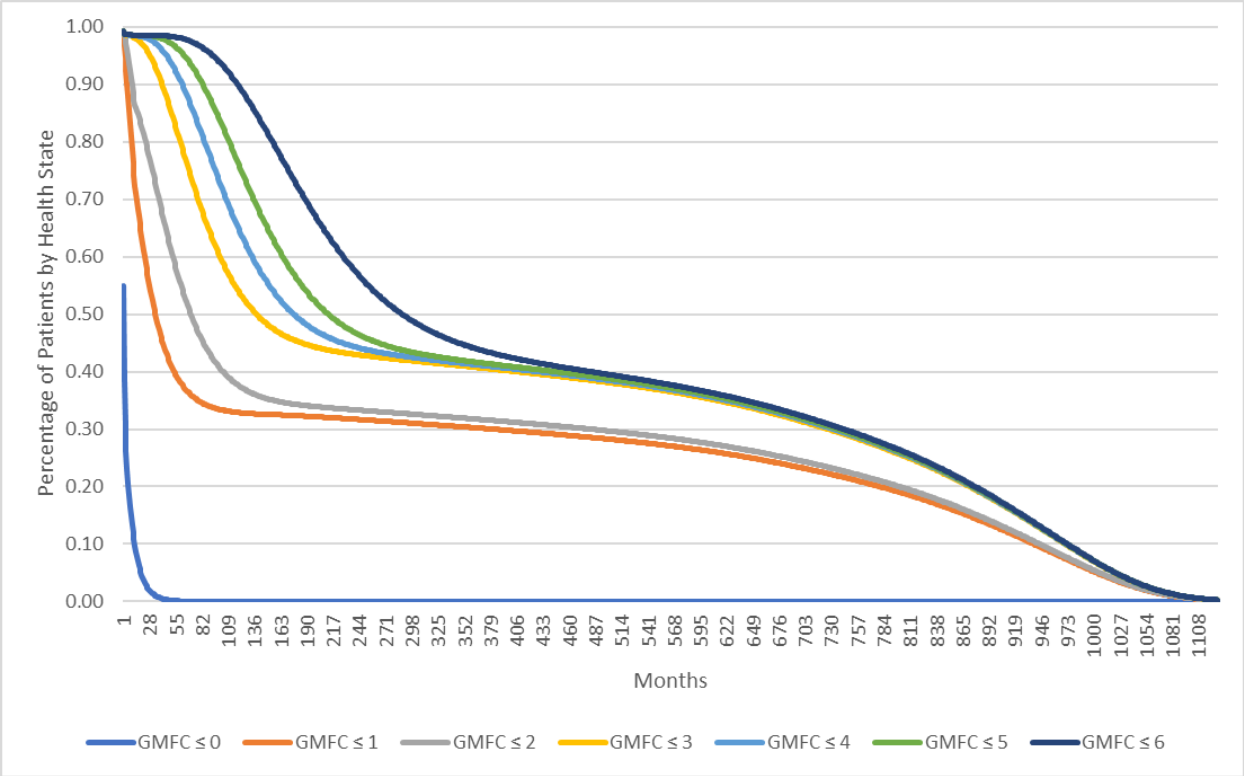


Figure E3.6 Disease Progression for arsa-cel, Early symptomatic EJ-MLD



E4. Sensitivity Analyses

To demonstrate the effects of uncertainty on both costs and health outcomes, we varied input parameters using available measures of parameter uncertainty (i.e. standard errors) or reasonable ranges to evaluate changes in cost per additional QALY for arsa-cel compared to usual care. The tornado diagram (Figure E4.1) and ranges of inputs and resultant incremental cost-effectiveness ratios (Table E4.1) from the health care sector showed the most influential inputs were the placeholder price of arsa-cel, stabilization period, and the time until arsa-cel had treatment benefit in the stable partial responders. The tornado diagram from the modified societal perspective is presented in Figure E4.2 and results in Table E4.2. Probabilistic sensitivity analyses were also performed by jointly varying all model parameters over 1000 simulations, then calculating 95% credible range estimates for each model outcome based on the results, as well as the proportion of simulations that were cost-effective at commonly used willingness-to-pay thresholds. The results are shown in Tables E4.3 and E4.4.

Figure E4.1. Tornado Diagram from the Health Care Sector Perspective for Cost per QALY gained

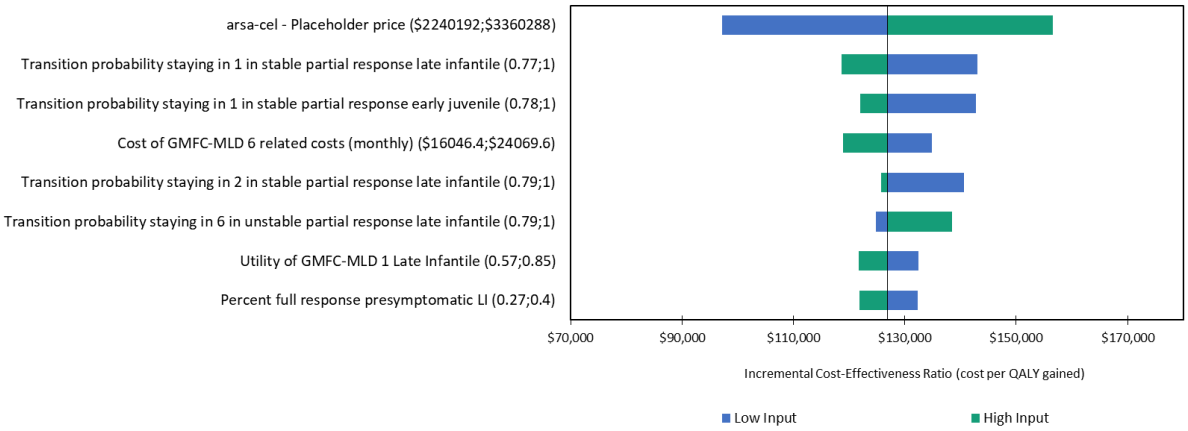


Table E4.1. Tornado Diagram Inputs and Results for Arsa-cel versus Usual Care from the Health Care Sector Perspective for Cost per QALY Gained

	Lower Incremental CE Ratio	Upper Incremental CE Ratio	Lower Input*	Upper Input*
Arsa-cel – Placeholder Price	97,000	157,000	2,240,000	3,360,000
Transition Probability Staying in GMFC-MLD State 1 in Stable Partial Responders, Late Infantile	119,000	143,000	0.77	1.00
Transition Probability Staying in GMFC-MLD State 1 in Stable Partial Responders, Early Juvenile	122,000	143,000	0.78	1.00
Cost of GMFC-MLD State 6 (Monthly)	119,000	135,000	16,000	24,000
Transition Probability Staying in GMFC-MLD State 2 in Stable Partial Responders, Late Infantile	126,000	141,000	0.79	1.00
Transition Probability Staying in GMFC-MLD State 6 in unstable partial response LI	125,000	139,000	0.79	1.00
Utility of GMFC-MLD 1, Late Infantile	122,000	132,000	0.57	0.85
Percent Full Response, Presymptomatic LI	122,000	132,000	0.27	0.40

CE: cost-effectiveness, EJ: early juvenile, LI: late infantile

*Note lower input may reflect either upper or lower incremental CE ratio value depending on the direction that the input has on the ICER output.

Figure E4.2. Tornado Diagram from the Modified Societal Perspective for Cost per QALY Gained

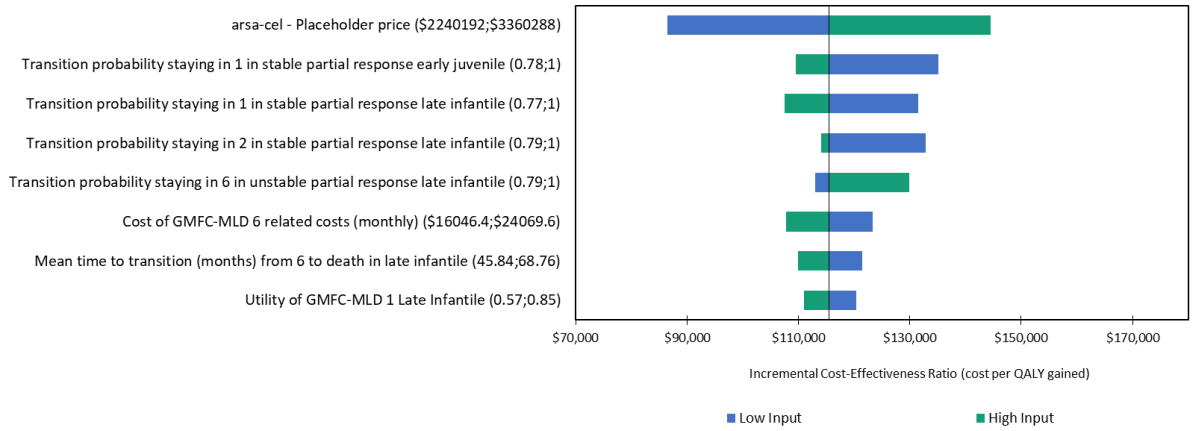


Table E4.2. Tornado Diagram Inputs and Results for Arsa-cel versus Usual Care from the Modified Societal Perspective for Cost per QALY Gained

	Lower Incremental CE Ratio	Upper Incremental CE Ratio	Lower Input*	Upper Input*
Arsa-cel – Placeholder Price	86,000	145,000	2,240,000	3,360,000
Transition Probability Staying in GMFC-MLD State 1 in Stable Partial Responders, Early Juvenile	110,000	135,000	0.78	1.00
Transition Probability Staying in GMFC-MLD State 1 in Stable Partial Responders, Late Infantile	107,000	132,000	0.77	1.00
Transition Probability Staying in GMFC-MLD State 2 in Stable Partial Responders, Late Infantile	114,000	133,000	0.79	1.00
Transition Probability Staying in GMFC-MLD State 6 in Unstable Partial Responders, Late Infantile	113,000	130,000	0.79	1.00
Cost of GMFC-MLD Stage 6 (Monthly)	108,000	123,000	16,000	24,000
Mean Time to Transition (Months) From GMFC-MLD State 6 to Death, Late Infantile	110,000	121,000	46	69
Utility of GMFC-MLD State 1, Late Infantile	111,000	120,000	0.57	0.85

CE: cost-effectiveness, EJ: early juvenile, LI: late infantile

*Note lower input may reflect either upper or lower ICER value depending on the direction that the input has on the ICER output.

Table E4.3. Probabilistic Sensitivity Analysis Cost per QALY Gained Results: arsa-cel versus Usual Care

	Cost Effective at $50,000 per QALY Gained	Cost Effective at $100,000 per QALY Gained	Cost Effective at $150,000 per QALY Gained	Cost Effective at $200,000 per QALY Gained
Health Care Sector Perspective				
Arsa-cel	0%	0.01%	97.20%	100%
Modified Societal Perspective				
Arsa-cel	0%	4.1%	99.6%	100%

arsa-cel: atidarsagene autotemcel, QALY: quality-adjusted life year

Table E4.4. Probabilistic Sensitivity Analysis Cost Per evLY Gained Results: arsa-cel versus Usual Care

	Cost Effective at $50,000 per evLY Gained	Cost Effective at $100,000 per evLY Gained	Cost Effective at $150,000 per evLY Gained	Cost Effective at $200,000 per evLY Gained
Health Care Sector Perspective				
Arsa-cel	0%	6.6%	100%	100%
Modified Societal Perspective				
Arsa-cel	0%	49.5%	100%	100%

arsa-cel: atidarsagene autotemcel, evLY: equal value life year

E5. Scenario Analyses

We conducted several scenario analyses to examine uncertainty and potential variation in the findings. The scenarios are presented below and the findings are presented in Tables E5.1 and E5.2. Scenario 6 for threshold analyses using the rescaled non-negative utility values are presented in Tables E5.3 and E5.4.

1. Undiscounted costs and outcomes.
2. An optimistic and conservative assumption regarding the benefit of treatment. For arsa-cel, this translated to a stabilization period of 50 years and 5 years for the optimistic and conservative scenarios, respectively.
3. Rescaled utility estimates that did not allow for negative utility values.
4. 50/50 shared savings in which 50% of lifetime health care cost offsets from a new treatment are assigned to the health care system instead of being assigned entirely to the new treatment
5. A consistent caregiver disutility regardless of disease severity

6. Threshold analyses to calculate the price needed to meet commonly accepted cost-effectiveness thresholds for QALYs gained and evLY gained using the rescaled non-negative utility values

Table E5.1. Scenario Analysis Results (Total Outcomes)

Health	Drug Cost*	Total Cost	QALYs	evLYs	LYs
Scenario 1: Undiscounted costs and outcomes					
Health Care Sector Perspective					
Arsa-cel	$2,800,000	$4,088,000	42.64	50.03	60.09
Usual Care	$0	$1,379,000	-0.91	-0.91	8.80
Modified Societal Perspective					
Arsa-cel	$2,800,000	$4,318,000	41.48	50.03	60.09
Usual Care	$0	$1,720,000	-2.11	-2.11	8.80
Scenario 2: Optimistic assumption of treatment benefit (50 years)					
Health Care Sector Perspective					
Arsa-cel	$2,800,000	$3,466,000	18.83	21.31	26.09
Usual Care	$0	$1,104,000	-0.51	-0.51	7.44
Modified Societal Perspective					
Arsa-cel	$2,800,000	$3,572,000	18.31	21.31	26.09
Usual Care	$0	$1,383,000	-1.49	-1.49	7.44
Scenario 2: Conservative assumption of treatment benefit (5 years)					
Health Care Sector Perspective					
Arsa-cel	$2,800,000	$3,503,000	18.10	20.77	25.47
Usual Care	$0	$1,104,000	-0.51	-0.51	7.44
Modified Societal Perspective					
Arsa-cel	$2,800,000	$3,620,000	17.55	20.77	25.47
Usual Care	$0	$1,383,000	-1.49	-1.49	7.44
Scenario 3: Rescaled utility estimates					
Health Care Sector Perspective					
Arsa-cel	$2,800,000	$3,493,000	18.63	21.04	25.66

Usual Care	$0	$1,104,000	1.33	1.33	7.44
Modified Societal Perspective					
Arsa-cel	$2,800,000	$3,607,000	18.08	21.04	25.66
Usual Care	$0	$1,383,000	0.35	0.35	7.44
Scenario 4: 50/50 shared savings					
Health Care Sector Perspective					
Arsa-cel	$2,800,000	$3,884,000	18.32	20.94	25.66
Usual Care	$0	$1,104,000	-0.51	-0.51	7.44
Modified Societal Perspective					
Arsa-cel	$2,800,000	$3,998,000	17.78	25.66	25.66
Usual Care	$0	$1,383,000	-1.49	-1.49	7.44
Scenario 5: Alternative caregiver disutilities					
Modified Societal Perspective					
Arsa-cel	$2,800,000	$3,607,000	17.34	20.94	25.66
Usual Care	$0	$1,383,000	-0.99	-0.99	7.44

arsa-cel: atidarsagene autotemcel, evLY: equal value life year, LY: life year, QALY: quality-adjusted life year
*Based on placeholder price

Table E5.2. Scenario Analysis Results (Incremental Cost-Effectiveness Ratios)

Scenario 1: Undiscounted Costs and Outcomes	Treatment	Comparator	Cost per QALY Gained	Cost per evLY Gained	Cost per life year Gained
Health Care Sector Perspective					
	Arsa-cel	Usual care	$62,000	$53,000	$53,000
Modified Societal Perspective					
	Arsa-cel	Usual care	$60,000	$50,000	$51,000
Scenario 2: Optimistic Assumption of Treatment Benefit	Treatment	Comparator	Cost per QALY Gained	Cost per evLY Gained	Cost per life year Gained
Health Care Sector Perspective					
	Arsa-cel	Usual care	$122,000	$108,000	$127,000
Modified Societal Perspective					
	Arsa-cel	Usual care	$111,000	$96,000	$117,000
Scenario 2: Conservative Assumption of Treatment Benefit					
Health Care Sector Perspective					
	Arsa-cel	Usual care	$129,000	$113,000	$133,000
Modified Societal Perspective					
	Arsa-cel	Usual care	$118,000	$101,000	$124,000
Scenario 3: Rescaled Utility Estimates					
Health Care Sector Perspective					
	Arsa-cel	Usual care	$138,000	$121,000	$131,000
Modified Societal Perspective					
	Arsa-cel	Usual care	$125,000	$108,000	$122,000
Scenario 4: 50/50 Shared Savings					
Health Care Sector Perspective					
	Arsa-cel	Usual care	$148,000	$130,000	$153,000
Modified Societal Perspective					
	Arsa-cel	Usual care	$136,000	$117,000	$144,000
Scenario 5: Alternate Caregiver Disutilities					
Modified Societal Perspective					
	Arsa-cel	Usual care	$121,000	$101,000	$122,000

Table E5.3. QALY-Based Threshold Analysis Results Using Rescaled Utilities

	Unit Price to Achieve $50,000 per QALY Gained	Unit Price to Achieve $100,000 per QALY Gained	Unit Price to Achieve $150,000 per QALY Gained	Unit Price to Achieve $200,000 per QALY Gained
Health Care Sector Perspective				
Arsa-cel	$1,276,000	$2,141,000	$3,006,000	$3,871,000
Modified Societal Perspective				
Arsa-cel	$1,462,000	$2,349,000	$3,235,000	$4,112,000

QALY: quality-adjusted life-year

Table E5.4. evLY-Based Threshold Analysis Results Using Rescaled Utilities

	Unit Price to Achieve $50,000 per evLY Gained	Unit Price to Achieve $100,000 per evLY Gained	Unit Price to Achieve $150,000 per evLY Gained	Unit Price to Achieve $200,000 per evLY Gained
Health Care Sector Perspective				
Arsa-cel	$1,397,000	$2,383,000	$3,369,000	$4,355,000
Modified Societal Perspective				
Arsa-cel	$1,610,000	$2,645,000	$3,679,000	$4,714,000

evLY: equal-value life-year

E6. Model Validation

Model validation followed standard practices in the field. We tested all mathematical functions in the model to ensure they were consistent with the report (and supplemental Appendix materials). We also conducted sensitivity analyses with null input values to ensure the model was producing findings consistent with expectations. Further, independent modelers tested the mathematical functions in the model as well as the specific inputs and corresponding outputs.

Model validation was also conducted in terms of comparisons to other model findings. We searched the literature to identify models that were similar to our analysis, with comparable populations, settings, perspective, and treatments. As part of ICER's efforts in acknowledging modeling transparency, we shared the model with the relevant manufacturer for external verification around the time of publishing the draft report for this review.

Prior Economic Models

We found one prior cost-effectiveness model for arsa-cel in MLD that the manufacturer developed and used in prior HTA submissions to FINOSE and NICE.[21-23] An analysis was conducted by the manufacturer from a US payer perspective (poster presentation), which reported an incremental QALY gain of more than 30 compared to best supportive care from the modified societal

perspective.[21] In our model for the base case from the modified societal perspective, arsa-cel resulted in 18 QALYs gained compared to usual care. There are several potential reasons for this difference. The reason that likely had the most impact was how the treatment benefit and duration were implemented. The manufacturer assumed a stabilization period of 50 years after which patients progressed at a rate similar to the unstable partial responders. In our model, we assumed a stabilization period of 12 years after which patients reverted to the unstable partial responder state at a monthly probability of 0.02%. Furthermore, different sets of disutilities were used to capture quality of life impacts on caregivers. Additionally, different discount rates were used (3.0% versus 1.5%) for cost and outcomes).

F. Potential Budget Impact: Supplemental Information

Methods

We used results from the same model employed for the cost-effectiveness analyses to estimate total potential budget impact. Potential budget impact was defined as the total differential cost of using each new therapy rather than relevant existing therapy for the treated population, calculated as differential health care costs (including drug costs) minus any offsets in these costs from averted health care events. All costs were undiscounted and estimated over one- and five-year time horizons. The five-year timeframe was of primary interest, given the potential for cost offsets to accrue over time and to allow a more realistic impact on the number of patients treated with the new therapy.

The potential budget impact analysis included the candidate populations eligible for treatment. To estimate the size of the potential candidate populations for treatment, we used inputs for the number of live births in the US per year (2021 estimate of 3,659,289)[33] and an incidence of 1/100,000 live births resulting in 37 individuals born with MLD in the US per year or 185 individuals over five years. The focus of this review is for patients with late infantile and early juvenile (pre-symptomatic and early symptomatic), which represents approximately 40-60% (74 to 111) and 35% (65) of individuals born with MLD, respectively, based on manufacturer-submitted estimates. Given that universal screening is not currently in place, it is anticipated that only a fraction of these cases will be detected. The manufacturer estimated that 32% of patients (LI: 24 to 36; EJ-PS: 21) will be detected based on a family history (i.e., children of parents who have already had an affected child), and 20% (13) of patients who are early symptomatic will be diagnosed with enough time to be eligible for treatment. Applying these sources results in estimates of 58 to 70 eligible patients in the US over five years. We used the upper end of this range, 70 patients over five years. For the purposes of this analysis, we will assume that 20% of these patients would initiate treatment in each of the five years, or 14 patients per year. It is important to note that the number of eligible patients is likely to be higher in the presence of a newborn screening program which would increase the potential budgetary impact of arsa-cel. Assuming an incidence of 1/40,000 live births, for example, suggests that the eligible patient population in the US could be as high as 91 patients per year, or 457 patients over 5 years.

ICER's methods for estimating potential budget impact are described in detail elsewhere and have recently been updated.[34,65] The intent of our revised approach to budgetary impact is to document the percentage of patients that could be treated at selected prices without crossing a budget impact threshold that is aligned with overall growth in the US economy.

Briefly, we evaluate a new drug that would take market share from one or more drugs and calculate the blended budget impact associated with displacing use of existing therapies with the new intervention. In this analysis, we assumed that no standard of care treatments would be displaced by the entrance of arsa-cel because existing care is largely supportive. Supportive care may include non-disease modifying pharmacologic or non-pharmacologic treatment to manage symptoms.

Using this approach to estimate potential budget impact, we then compared our estimates to an updated budget impact threshold that represents a potential trigger for policy mechanisms to improve affordability, such as changes to pricing, payment, or patient eligibility. As described in ICER's methods presentation (Value Assessment Framework), this threshold is based on an underlying assumption that health care costs should not grow much faster than growth in the overall national economy. From this foundational assumption, our potential budget impact threshold is derived using an estimate of growth in US gross domestic product (GDP) +1%, the average number of new drug approvals by the FDA over the most recent two-year period, and the contribution of spending on retail and facility-based drugs to total health care spending.

For 2022-2023, therefore, the five-year annualized potential budget impact threshold that should trigger policy actions to manage access and affordability is calculated to total approximately $777 million per year for new drugs.

Results

Figure F1 illustrates the cumulative per patient potential budget impact for arsa-cel compared to usual care. At arsa-cel's placeholder price ($2,800,240 per treatment course), the average annual budget impact per patient was $2,956,915 in Year one with cumulative net costs increasing to $6,513,943 in Year five. Annual net costs decreased in years two through five due to higher non-intervention costs for the comparator compared to arsa-cel.

Figure F1. Cumulative Net Cost per Patient Treated with Arsa-cel at Placeholder Price

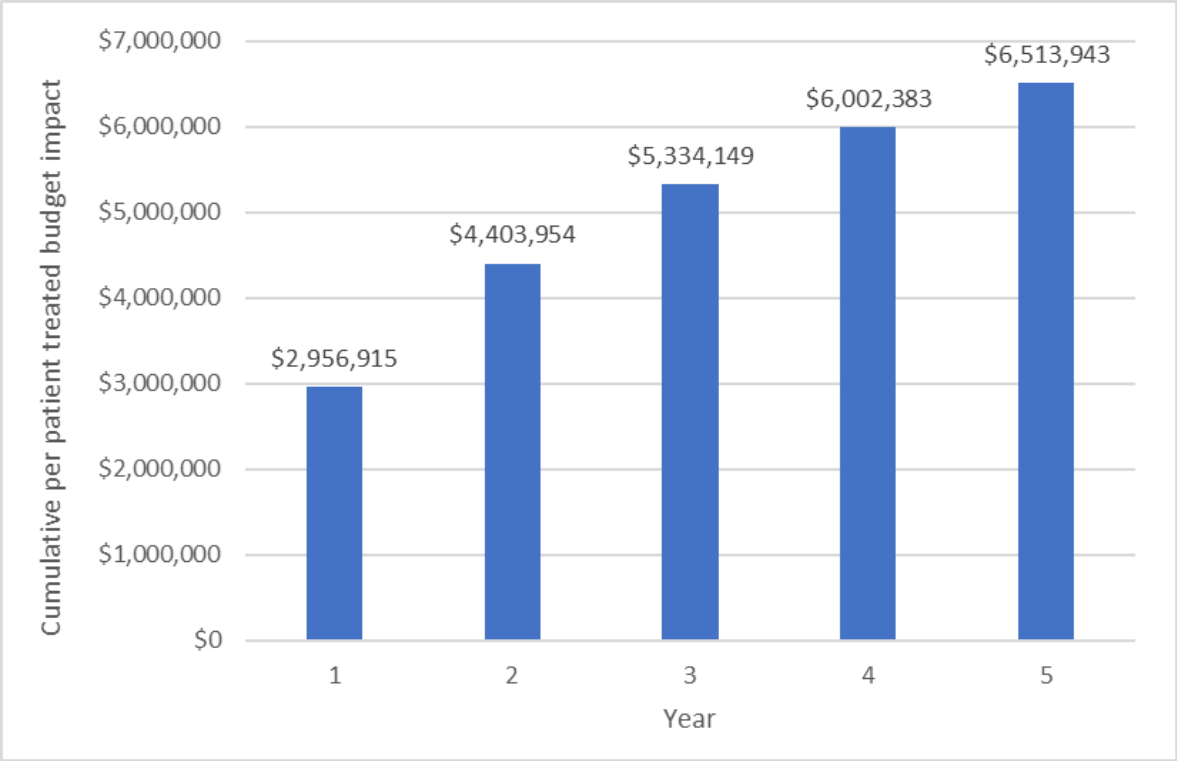


Table F1. illustrates the per-patient budget impact calculations in more detail, based on the placeholder price ($2,800,240), and the prices to reach $150,000, $100,000, and $50,000 per QALY for arsa-cel ($3,235,771, $2,294,241, and $1,352,712, respectively).

Table F1. Per-Patient Budget Impact Calculations Over a Five-year Time Horizon

	Average Annual Per Patient Budget Impact			
	At Placeholder Price	**$150,000/QALY**	**$100,000/QALY**	**$50,000/QALY**
Arsa-cel	$1,302,800	$1,501,600	$1,071,800	$641,600

QALY: quality-adjusted life year

G. Supplemental Policy Recommendations

Payers

Coverage Criteria: General

Given the high cost of arsa-cel and the uncertain long-term outcomes, it is reasonable for payers to use prior authorization as a component of coverage. Prior authorization criteria for arsa-cel should be based on clinical evidence and input from clinical experts and patient groups. The process for authorization should also be clear, accessible, efficient, and timely for providers. Perspectives on specific elements of cost sharing and coverage criteria within insurance coverage policies are discussed below. Relevant Fair Access Design Criteria set out in ICER's previous work are included.

Drug-Specific Coverage Criteria: Arsa-cel

Although MLD is an ultra-rare disease, treatment with arsa-cel is likely to have a very high one-time cost and thus payers will develop prior authorization criteria and consider other limits on utilization.

None of these limits, however, should undermine the tenets of fair access to which all patients have a fundamental right.[35] To explore the appropriate application of evidence to coverage policy, and to reflect the views of patient experts and clinicians on specific ways that payers might appropriately use coverage policy to manage resources prudently, we present the following perspectives on specific elements of cost sharing and coverage criteria for arsa-cel.

Coverage Criteria

- **Diagnosis:** Diagnosis of MLD is based on a combination of clinical presentation, biochemical testing (e.g., arylsulfatase A enzyme activity, urine sulfatide levels), brain MRI, and/or genetic testing for mutations in the ARSA gene. Diagnosis of presymptomatic disease will either be through testing of siblings of a previously affected and diagnosed child or through newborn screening. Widespread newborn screening will detect variants of uncertain significance; these variants may lead to difficult decisions about appropriate treatment and insurance coverage, since it is not known whether some genetic mutations may lead to a later onset or possibly milder form of the disease for which the harms of gene therapy may outweigh any benefits. If payers require genetic testing to establish diagnosis, they should have mechanisms to ensure that there are no delays in obtaining genetic testing and results, and to not require repeated documentation of genetic testing results.

- **Age:** It is unclear whether the FDA will specify an age or weight range in its approved indication for arsa-cel, so payers may be left to decide whether to include some threshold in coverage criteria. Clinical experts advised that there may be a minimum weight (e.g., 5-7 kg) to undergo treatment safely, but if treatment decisions are reserved for experts at Centers of Excellence it may be reasonable for payers to leave age and weight criteria to the discretion of these experts. If payers do set age or weight criteria based on the clinical spectrum of patients in the pivotal trial, they should ensure that clinicians have efficient mechanisms for seeking coverage exceptions for patients who are near whatever thresholds are set.

- **Clinical eligibility**: Treatment with arsa-cel will likely be restricted to the populations included in the clinical trials: presymptomatic late-infantile, presymptomatic early juvenile, and early symptomatic early juvenile MLD. There is no current evidence that children with late juvenile or adult MLD should be treated with arsa-cel; ongoing trials will provide data on the efficacy and safety of arsa-cel treatment for the late juvenile population.

    - Payers need to consider whether to establish criteria for the diagnosis of late-infantile or early juvenile MLD, particularly for presymptomatic patients. According to clinical experts and clinical studies, there is high concordance between genotype and phenotype, particularly among siblings,[45] and thus payers will need to decide whether documentation of a genotype known to be associated with late-infantile or early juvenile MLD is necessary or whether clinician attestation will suffice. In addition, as noted earlier, there will be new variants of uncertain significance that will emerge with newborn screening, and payers need to be ready to either quickly update their criteria when new evidence becomes available or rely on clinician attestation for diagnosis.

    - Payers will also need to consider whether to use a specific definition of early symptomatic early juvenile MLD. Clinical experts advised that it is reasonable to apply the clinical trial criteria of GMFC-MLD 0-1 and IQ≥85; however, payers will need to have a process to consider exceptions for impairments due to non-MLD comorbidities (e.g., motor impairments that may be due to comorbid cerebral palsy rather than MLD) or for patients close to the IQ cutoff.

- **Exclusion criteria**: In the clinical trials, children who received treatment with hematopoietic stem cell transplant (HSCT) within the last six months and with residual cells of donor origin were excluded from the trial. Given that treatment with arsa-cel includes autologous HSCT, it is reasonable for payers to adopt this exclusion for coverage.

- **Dose:** The dose of arsa-cel is weight-based and should follow dosing in the clinical trials.

- **Duration of coverage and renewal criteria**: This is a one-time treatment; there is no evidence that repeat treatments are indicated.

- **Provider restrictions**: Clinical experts agreed that treatment should be done at specialized centers. Because MLD is a rare disease, specialty clinicians are better suited to identify patients who are most likely to benefit, provide sufficient information for caregivers to make a well-informed decision about treatment, and monitor for response and side effects.

Step Therapy

No step therapy is appropriate for treatment of the early-onset forms of MLD.

For the early-onset forms of MLD, clinical experts and clinical practice guidelines agreed that HSCT has inferior clinical outcomes compared with arsa-cel. Since arsa-cel is most effective before symptoms are noted and progression of disease is often rapid after onset of symptoms, it is not appropriate for payers to require evaluation for or treatment with HSCT in the late infantile and early juvenile forms of HSCT prior to treatment with arsa-cel.

H. Public Comments

This section includes summaries of the public comments prepared for the CTAF Public Meeting on Friday, September 29, 2023. These summaries were prepared by those who delivered the public comments at the meeting and are presented in order of delivery. One speaker did not submit summary of their public comments.

A video recording of all comments can be found here, beginning at minute 00:00:30. Conflict of interest disclosures are included at the bottom of each statement for each speaker who is not employed by a pharmaceutical manufacturer.

Kent Christopherson, Ph.D.
Executive Director & Head, Global Medical Affairs, Orchard Therapeutics

Thank you for giving us the opportunity to participate in this public meeting. We truly appreciate the significant amount of work that ICER and its associates have conducted. As the Evidence Report highlights, early-onset metachromatic leukodystrophy (MLD) is a devastating, relentlessly progressive, fatal disease, underscoring the need for access to disease-modifying therapies, such as arsa-cel.

The significant impact of MLD on the health-related quality of life has been captured sufficiently by the revised utility value set represented in the current Evidence Report. Specifically, the MLD utility values demonstrate face validity as they align with other rare progressive severe disease analogs, such as SMA, CLN2, MPS-IVA, X-ALD, and DMD, that have motor and neurocognitive pathology. The Evidence Report also reflects that the caregiver burden increases as the disease worsens. Consequently, caregiver disutilities in the Evidence Report have been appropriately updated to reflect this.

The standard of care in the United States for early-onset (late infantile and early juvenile subtypes) MLD is supportive care, consisting of medications and procedures to manage the symptoms of MLD and do not target or have any effect on the underlying cause of disease. This is demonstrated in the natural history cohort of early-onset MLD patients where all late infantile patients progressed by age 5, and all early juvenile patients progressed by approximately age 10, to a state of complete loss of locomotion and trunk control (GMFC-MLD level ≥5) or death.

The outcomes of the natural history data are in stark contrast to the clinical trial data for arsa-cel, specifically:

- 94% of treated pre-symptomatic late infantile MLD patients retained locomotion (GMFC-MLD 0, 1, or 2) at last follow-up, as compared to none in the natural history cohort at the same age. All these natural history patients have exhibited severe motor impairment (GMFC-MLD level of ≥5) or death. Furthermore, the longest follow-up of more than 12 years in the earliest arsa-cel treated pre-symptomatic late infantile patient extends beyond the age at which nearly all the corresponding natural history children have sadly passed away.
- All surviving treated pre-symptomatic early juvenile MLD patients maintained mobility similar to their healthy peers (GMFC-MLD 0) and with cognitive function typical for age (performance standard score > 70). Additionally, the longest follow-up in the earliest arsa-cel treated pre-symptomatic early juvenile patient extends beyond the age at which nearly all the corresponding natural history children have become severely disabled or sadly passed away.
- In addition to slowing or stopping motor function decline, one of the key benefits of arsa-cel treatment in early symptomatic early juvenile MLD patients is the preservation of cognitive function, even in patients who have incurred some motor dysfunction due to their early symptomatic status at time of treatment. For example, although some treated patients have gross motor function that has stabilized (GMFC-MLD 3 or 4), meaning their functional status may involve the need for a wheelchair, these same patients have a cognitive function typical for age (performance standard score > 70) thereby allowing them to retain their independence, such as attending school or university and interacting with their peers. These arsa-cel treated children are all associated with a better clinically meaningful outcome than the corresponding natural history patients who have exhibited severe cognitive impairment (standard performance score ≤ 55).

Finally, Orchard agrees with the revised assumptions around the long-term durability of effect for patients classified as full and stable partial responders in the model. The hematopoietic stem cell gene therapy (HSC-GT) technology platform utilized by arsa-cel is specifically designed to result in a prolonged durable treatment effect. This is because the mechanism of action of arsa-cel leverages the use of the patient's own autologous hematopoietic stem cells, *ex vivo* genetic correction of the self-renewing hematopoietic stem cells, ability of these cells to permanently engraft in the patient, and capacity of these cells to cross the blood-brain barrier and deliver therapeutic benefit by way of enzyme expression in the central and peripheral nervous system. Consequently, after successful and stable engraftment of arsa-cel, restoration of ARSA activity along with the persistent clinically meaningful benefit is expected.

The ongoing follow-up for arsa-cel represents one of the longest follow-up periods in gene therapy clinical development, extending more than 12 years in the earliest treated patient. We believe that arsa-cel continues to provide a favorable benefit / risk profile with consequently significant value not only to the patient, but also the wider healthcare system and MLD community.

Maria Kefalas, Ph.D.
Founder, Cure MLD

On behalf of Cure MLD, the following video was shared as their oral public comment about the patient experience of gene therapy for MLD: https://vimeo.com/583326581/28b73a1dcd

Cure MLD has received grants from Bluebird Bio, Homology Medicines, Orchard Therapeutics, Takeda Pharmaceuticals, and Passage Bio, Inc.

Victoria Rasberry
MLD Parent

Hello, my name is Victoria and I am the mother of two beautiful children, Addi and Oliver, with Metachromatic Leukodystrophy. As a parent, when your child is born you dream about the future of your children's lives, such as the first day of school, prom, graduation, what their future careers will look like, who they will marry, their wedding day, and your future grandchildren. When Addi was born I had all of those dreams for her, and her first year of life was blissful. She was incredibly smart, hitting milestones on time or before. She was walking, talking, showing us her sassy and funny personality and then the monster that is MLD entered our lives. She began to fall when she was walking, something that she never had trouble with before. This began our 9 month odyssey to find out what was wrong with our baby girl, all the while she was losing more and more of the milestones she had previously mastered. Countless specialist visits, MRIs, intensive physical therapy, and multiple wrong diagnoses. No one could tell us what was wrong. Not until the day after her second birthday, after the second MRI of her brain, and third MRI of her spine. Our baby girl was dying. Not only that but she would be trapped inside a body fighting against her at the age of 2 as she would continue to lose all of her abilities. I would no longer hear I love you from my baby girl. She could no longer give us a hug or kiss us. The day we first heard the words Metachromatic Leukodystrophy is the day all of our hopes and dreams for Addi shattered. Addi has always loved animals, especially big farm animals. When she was little I used to believe she would be a vet for farm animals. But that is not her fate. Soon after diagnosis she would begin to have seizures, and would begin to have chronic respiratory failure. She struggles to breathe on a daily basis, has to use a ventilator, and has to have respiratory therapies every 4 hours. She has 24 hour nursing care. She is a PICU baby and we have gotten to know our local PICU staff very well. She cannot attend school, she will never go to prom or graduate, she will never be married, never have children, and never live to see her dream of becoming a vet come true. She will never get to fully live her life. She will live out her few short years here trapped inside herself.

Oliver, however, does not have that same fate. He was given a miracle, a chance to live his life. Oliver was tested right after birth, confirming the MLD diagnosis. At 6 months old, after raising $500,000, Oliver and I traveled to Italy where he received OTL-200. Oliver's rebirthday (the day he

was infused) was June 25, 2021 when he was 8 months old. Oliver will be 3 in 22 days. He has shown absolutely no signs of regression. In fact, he has continued to flourish and thrive. Each day he is learning and gaining new words, new skills, new everything!! He is not nonverbal, he is not tied down to machines, and he is able to do things we only dreamed of for Addi. We are not afraid to dream about Oliver's future. He will be starting school next month, and we are already excited and dreaming about his first day of kindergarten, his elementary, middle, and high school years, about what extracurriculars he will engage in, his graduation, and his prom. Things we will never get to experience with Addi. Oliver will get to live his life in a way Addi never could. He is walking, where Addi was immobile, he is talking and telling us I love you, where Addi could only blink, he is exploring, where we had to explore for Addi and convey our experiences. He is living the life of a child, not a patient.

Over the last 4 years, the MLD community has gained 56 angels and counting. 56 children, whose hopes and dreams will never come to fruition. 56 children that will never to get to experience life. 56 families now lost without their loved one. This is Addi's future, but it is not Oliver's. My hope and dream is that other families do not have to suffer Addi's fate. Through newborn screening, babies can be diagnosed at birth just like Oliver, and be granted the same life changing therapy. Every MLD child should be afforded the opportunity to not just exist but live.

No conflicts to disclose.

Dean Suhr, BS
President, MLD Foundation

Greetings,

Thank you for including MLD Foundation throughout the development of this document as an Expert Reviewer and transparently responding to not only our feedback but also the feedback of other informed MLD experts. We appreciate the detailed and thorough nature of the ICER analysis.

Qualifications for this response

I am a MLD dad. After a 6-year diagnostic and misdiagnosis odyssey, two of my three children were diagnosed with late juvenile MLD. I lost my youngest daughter, Darcee, at age 10 in 1995 due to GVHD reactions after a successful BMT. Lindy, without therapy, has outlived the published (1995) expectation of dying in her early 20s…. she is fully disabled, and we just celebrated her 43rd birthday in the ocean waves around Maui. We're blessed by this but also have first-hand knowledge that publications do not always tell the whole story of MLD.

I have decades of MLD family compassion and advocacy leadership … my wife and I launched MLD

Foundation in 2001 after co-hosting the world's first MLD Family Conference® in 1999. I've held key roles at Global Genes, Genetic Alliance, and Everylife/RDLA. I encouraged the founding of Haystack Project.

MLD Foundation has over 700 patients in its profile database. We have personally met hundreds of patients at gatherings, conferences, and events from Australia to Tokyo, across the US, Canada, Germany, the UK, and other parts of Europe. We've met and traveled the MLD journey with more patients than anyone else on the planet, including – with all due respect, the KOLs, doctors, and researchers.

We've worked with over a dozen biopharma's over the past 20+ years, including meeting and starting to work with the arsa-cel research team (pre-biopharma) in 2005.

We've been actively engaged in clinical trials, newborn screening, and policy for nearly 2 decades. Of recent, we've been focused on newborn screening for the earliest patient identification and access & reimbursement to get patients treated.

Concerns about the review process

- Lack of direct engagement of long-term MLD CLINICAL care experts who are arm's length from the arsa-cel therapy under review (Escolar, Patterson, Adang, Jones, Kraegeloh-Mann, Groschel, Eichler, etc.) This is important because the comparison of arsa-cel is to the current standard of care, which is to optimize quality of life since there is no viable alternative therapy.
- How the ICER decisions made today can and will be updated or refined as data and market dynamics change (additional research, off-label use results, additional longevity of current patients, etc.).
- Scope and impact of ICER decisions
    - Use of QALYs as a metric … see PIPC comments
    - FIY, Orchard Therapeutics completed its BLA submission last month and has a March 18th PDUFA date. Today's decision is critical and timely for patients identified in 2024.
    - We don't want any patients who might benefit from therapy to be excluded because of ICER decisions … untreated MLD is not mild; it is painful and terminal in a timeframe shorter vs the clinical trial participants who have been living normal, essentially MLD- free lives.
    - The FDA controls the label. After approval, the doctors and payors control who gets therapy (on and off-label) - this is where ICER has an impact.
- Monte Carlo models

- I did not dig into the actual ICER models - trust those work as designed, *however,* these models are highly influenced by the data and assumptions you feed into them, specifically imputed ARSA values, and stability/longevity of therapy.

Concerns about key assumptions

- Harms
    - Three primary harms
        - Short-term harms were primarily due to busulfan conditioning
            - "There are harms from busulfan conditioning, including a risk of death, however, these are clearly outweighed by the benefits of treatment." (pg 19).
            - Arsa-cel is an autologous transplant … giving an opportunity to optimize and reduce conditioning regiments over time.
        - Transplant may accelerate progression during the time arsa-cel "takes over"
            - Newborn screening should eliminate the accelerated progression period with timely arsa-cel transplant in advance of the start of significant progression.
    - Early symptomatic might not have perfect outcomes. Newborn screening will eventually identify all patients before progression and eliminate all early symptomatic children.
- The benefits of newborn screening, which has been scientifically proven to work very well, need to be more heavily considered in the assessments.
- With all due respect and compassion for families –-
    - Future fertility concerns and cancer … deceased children (i.e. no therapy) are not fertile and can't get cancer.
    - Geographic access to therapy is a large but manageable logistical problem … nearly all families offered clinical trial enrollment in Italy were able to make that work – we can work out US geographic problems.
- The weighting of no therapy, i.e. death, needs to be increased – "Without effective treatments, the early-onset forms of MLD are devastating and rapidly fatal" (pg18). Death is harmful to patients, families, and society.

Cost-effectiveness depends on price and long-term durability

- It seems overly conservative to weigh the backward-looking 12 years rather than using trends to more highly weigh and model future-looking 15, 20, 25, or even 50 years – the

simulation can always be adjusted down with more data if or when we know the trends start to go negative.

    - Current model - stable 90% partial 70% alive at 35 years … you and I die at 1000+ months so MLD deceased at 1,000 months is normal.
    - Sensitive analysis should use a longer stability.
    - These changes will have a huge positive impact on the HBPB.

- There are prices reported for OTL-200 in the EU … the $2.8M placeholder was presumably established with awareness of the EU prices.
- Cost of arsa-cel will be a challenge for reimbursement (especially Medicaid across state lines and some private payors). However, it is ICER's responsibility to assess value, not to hesitate when the (demonstrated) positive net value involves big up-front numbers. Patient advocacy can and will address access issues.

Equity …

- We have primarily served those who come forth and self-identify. Newborn screening will proactively guide families to therapy, advocacy, other MLD families, and/or biopharma, and provide timely, accurate information.
- We must endeavor to expand our engagement with historically under-identified and under-diagnosed communities proactively… FDA approval, newborn screening, a positive ICER value outcome, and more culturally engaging approaches are key next steps to achieving greater equity.

EJ did not show as much benefit as LI

- Kaplan-Meier fig 3.2 & 3.3 … post-therapy EJ has slower progression than LI, yet the study period was the same … of course EJ does not show as dramatic results as LI. Please extrapolate the ES EJ chart for realistic natural history deaths

ARSA activity level

- Tables showed 5x to 124x ARSA activity improvement … but most LI's have zero or near zero, not 25.8.
- Compared to natural history … but carriers often have 10-15% of "normal" ARSA levels – it's not obvious that this reference was studied/included when valuing the impact of arsa- cel.

GMFC-MLD

- some LI progressed to higher GMFC and lower IQ while PS-EJ held steady.

    - Was this because those children did not access therapy soon enough to avoid progression that did not present clinically?
    - Again, NBS will optimize the earliest possible identification of new patients

Uncertainties & Controversies

- Single arm study bias … note that their non-treated peers are dead.
- GMFM score timing comparisons … arsa-cel children are in school and excelling … their non-treated peers are dead.
- What ARSA level is adequate … carriers were not studied/reported … general indications are half of normal is a carrier, 0-15% is affected (Normal 77 +/- 18 Carrier 43+/-4),
- Mild forms of MLD with unrecognized mutations … we met hundreds of MLD patients – we don't see any notable mild MLD. Will arsa-cel harm those patients – let's identify these patients and study them to determine the extent of this potential problem .. if true, we can use the sequencing that is part of the current NBS flow to recommend therapy or no therapy for these babies appropriately. (see 2023 Trinidad paper)
- Remember … "Without effective treatments, the early-onset forms of MLD are devastating and rapidly fatal" (pg 18)
- Treatment response and associated proportions
    - 12 yr stable, 1 year decline, 0.02% annual decline … should assume stable longer than 12 years.
    - 44% full response, ⅓ stable partial response, and 20% unstable partial response. NBS will, over time, move nearly all patients to full and partial response through earlier diagnosis and therapy.
- Value-Based Payment (VBP) contracts … drug companies "in the boat with the patients and payors" if the treatment does not meet milestones … rebates, refunds, etc.

MLD Foundation has received sponsorships from various biopharma companies for their annual family conference. Mr. Suhr has equity interests such as individual stocks, stock options, or other ownership interests in excess of $10,000 in Orchard Therapeutics.

I. Conflict of Interest Disclosures

Tables I1 through I3 contain conflict of interest (COI) disclosures for all participants at the Friday, September 29, 2023 Public meeting of Atidarsagene Autotemcel for Metachromatic Leukodystrophy.

Table I1. ICER Staff and Consultants and COI Disclosures

ICER Staff and Consultants*	
Josh Carlson, PhD, MPH, Professor, Department of Pharmacy, University of Washington	**Grace Lin, MD,** Medical Director for Health Technology Assessment, ICER
Sarah Emond, MPP, President-Elect, ICER	**Steven Pearson, MD, MSc,** President, ICER
Shahariar Mohammed Fahim, PhD, Research Lead, Evidence Synthesis, ICER	**Finn Raymond, BS**, Research Assistant, ICER
Kelsey Gosselin, MA, Program Manager, ICER	**Marina Richardson, PhD, MSc,** Senior Health Economist, ICER
Belen Herce-Hagiwara, BA, Senior Research Assistant	**David Rind, MD, MSc,** Chief Medical Officer, ICER
Yasmine Kayali, BA, Senior Program Coordinator, ICER	**Kangho Suh, PharmD, PhD,** Assistant Professor, University of Pittsburgh

*No conflicts of interest to disclose, defined as individual health care stock ownership (including anyone in the member's household) in any company with a product under study, including comparators, at the meeting in excess of $10,000 during the previous year, or any health care consultancy income from the manufacturer of the product or comparators being evaluated.

Table I2. CTAF Panel Member Participants and COI Disclosures

Participating Members of CTAF and New England CEPAC*	
Ralph Brindis, MD, MPH, MACC, FSCAI, FAHA, Clinical Professor of Medicine, UCSF	**Donald Kreis, JD,†** Consumer Advocate, New Hampshire Office of the Consumer Advocate
Robert Collyar, Patient Advocate, Breast Cancer; Board Member, Breast Cancer Action; Co-Founder, Clinical Trials Information Project	**Sei Lee, MD, MAS,** Associate Professor of Medicine, UCSF
Rena Fox, MD, Professor of Medicine, UCSF	**Greg Low, PhD, RPh,†** Program Director, MGPO Pharmacy Quality and Utilization Program, MGH
Jeffrey Hoch, PhD, Professor and Chief of the Division of Health Policy and Management, UC Davis	**Aaron Mitchell, MD, MPH,†** Assistant Attending, Memorial Sloan Kettering Cancer Center
Rebecca Kirch, JD,† Executive Vice President, Health Care Quality and Value for the National Patient Advocate Foundation (NPAF)	**Rita Redberg, MD, MSc, FACC,** Cardiologist and Professor of Medicine; Director of Women's Cardiovascular Services, UCSF
Jeff Klingman, MD, Chair of Neurology, Kaiser Permanente, Walnut Creek	**Jason Wasfy, MD, MPhil,†** Associate Professor, Harvard Medical School, MGH Heart Center; Director, Quality and Outcomes Research, MGH Heart Center
Stephen Kogut, PhD, MBA, RPh,† Professor of Pharmacy Practice, University of Rhode Island College of Pharmacy	

*No relevant conflicts of interest to disclose, defined as more than $10,000 in healthcare company stock or more than $5,000 in honoraria or consultancies during the previous year from health care manufacturers or insurers.
†Members of NE CEPAC

Table I3. Policy Roundtable Participants and COI Disclosures

Policy Roundtable Participant	Conflict of Interest
Laura Adang, MD, PhD, Assistant Professor of Neurology, Children's Hospital of Philadelphia	Dr. Adang is a consultant to Takeda Pharmaceuticals and Orchard Therapeutics. She is also a co-investigator on a Takeda clinical trial.
Francesca Fumagalli, MD, PhD, Neurologist, Pediatric Immunohematology Unit and Department of Neurology, IRCCS San Raffaele Hospital, Milan	Dr. Fumagalli is a sub investigator of clinical trials NCT01560182 and NCT03392987 and PI of clinical trial NCT04283227 using OTL-200 sponsored by Orchard Therapeutics. Dr. Fumagalli has received less than $5,000 in honoraria from Orchard Therapeutics and Takeda.
Stephen Jung, PharmD, Principal Pharmacist, Blue Shield of California	Stephen is a full-time employee of Blue California.
Maria Kefalas, PhD, Founder, Cure MLD; Professor, Saint Joseph's University	Cure MLD has received grants from Bluebird Bio, Homology Medicines, Orchard Therapeutics, Takeda Pharmaceuticals, and Passage Bio, Inc.
Julia Mahler, PharmD, Clinical Pharmacist, IPD Analytics	Julia is a full-time employee of IPD Analytics.
Paul Orchard, MD, Professor of Pediatric Blood and Marrow Transplantation and Cellular Therapy, University of Minnesota	Dr. Orchard's team offers expanded access to OLT-200 in association with Orchard Therapeutics for specific patients. He has received less than $5,000 in honoraria or consultancies from Orchard Therapeutics.
Francis Pang, MBA, SVP Global Market Access and International Geographic Expansion, Orchard Therapeutics	Francis is a full-time employee of Orchard Therapeutics.
Teryn Suhr, RN, Executive Director & Co-Founder, MLD Foundation	The MLD Foundation has received sponsorships from various biopharma companies for their annual family conference.