SMC2886

atidarsagene autotemcel dispersion for infusion (Libmeldy®)

Orchard Therapeutics Limited

07 August 2026

The Scottish Medicines Consortium (SMC) has completed its assessment of the evidence for the above product using the ultra-orphan framework:

Advice: following a submission through the ultra-orphan framework

atidarsagene autotemcel (Libmeldy®) is accepted for use within NHSScotland.

Indication under review: Treatment of metachromatic leukodystrophy (MLD) characterized by biallelic mutations in the arylsulfatase A (ARSA) gene leading to a reduction of the ARSA enzymatic activity:

- in children with late infantile or early juvenile forms, without clinical manifestations of the disease,
- in children with the early juvenile form, with early clinical manifestations of the disease, who still have the ability to walk independently and before the onset of cognitive decline.

In combined data from phase I/II studies and three early access programmes, atidarsagene autotemcel increased gross motor function scores in pre-symptomatic late infantile and in pre- and early symptomatic early juvenile MLD patients, when compared with a natural history cohort of patients with MLD.

This advice takes account of the views from a Patient and Clinician Engagement (PACE) meeting.

This advice applies only in the context of approved NHSScotland Patient Access Scheme (PAS) arrangements delivering the cost-effectiveness results upon which the decision was based, or PAS/ list prices that are equivalent or lower.

Chair
Scottish Medicines Consortium

1. Clinical context

1.1. Background

Atidarsagene autotemcel is an ex vivo genetically modified autologous $CD34^+$ haematopoietic stem and progenitor cell (HSPC) gene therapy.[1] $CD34^+$ cells (cells that make white blood cells) are extracted from the blood or bone marrow and are inserted with a gene that allows production of the arylsulfatase A (ARSA) enzyme. Following myeloablative conditioning, these modified $CD34^+$ cells are then administered to the patient where they grow and make normal white blood cells that can produce working ARSA. The ARSA helps to break down sulfatides in surrounding cells which controls the symptoms of the disease. Following successful and stable engraftment in the patient, the effects are expected to be persistent.[2] Atidarsagene autotemcel is intended for autologous use and should only be administered once, as an intravenous infusion. The minimum recommended dose is 3×10^6 $CD34^+$ cells/kg of body weight (body weight at the time of infusion); in clinical studies, doses up to 30×10^6 $CD34^+$ cells/kg have been administered. See Summary of Product Characteristics (SPC) for more details.[1]

1.2. Nature of condition

Metachromatic leukodystrophy is a rare autosomal recessive inherited lysosomal storage disease caused by mutations in the ARSA gene. These mutations result in deficiency of the corresponding ARSA enzyme that is responsible of breaking down sulfatide, a major component of oligodendrocyte in the central nervous system and Schwann cell myelin membrane in the peripheral nervous system. ARSA enzyme deficiency results in sulfatide accumulation, which leads, in the nervous system (and to a lesser extent in other organs such as the liver), to microglial damage, progressive demyelination, neurodegeneration, and subsequent loss of motor and cognitive functions and early death, especially in patients with early disease onset.[3]

The MLD disease spectrum can present in a variety of clinical forms that can be classified primarily based on the age of onset: late infantile (≤30 months), early juvenile (>30 months to <7 years), late juvenile (≥7 years to <17 years) and adult (≥17 years). Late infantile MLD (in which patients usually have almost no ARSA activity) is the most prevalent form. It has a predictable, aggressive and severe disease course that is characterised by progressive decline in motor and cognitive function with early death. Juvenile MLD (in which patients generally have some degree of ARSA activity) is characterised by a generally slower and more variable initial disease progression.[3]

In all forms, there is a pre-symptomatic stage with normal motor and cognitive development, followed by the onset of first symptoms and a developmental plateau period, which is short in early-onset forms. Then, inevitably follows a state where cerebral function is markedly reduced or lost and eventually an early death.[3] Retrospective analysis of MLD cases since 1921 showed that median survival for late infantile and juvenile patients was 2.7 and 9 years, respectively.[4]

The severe deterioration in the physical and cognitive condition of the patient is a substantial burden on their quality of life; patients often suffer from distressing symptoms including severe immobility and are wheelchair dependent making it difficult to complete activities of daily living. Loss of cognitive function affects many aspects of social functioning, limiting communication, social relationships and enjoyment of life. The impairments experienced by MLD patients are devastating for families and have a significant detrimental physical, emotional, psychosocial and financial impact on carers, who are often providing round-the clock care and must come to terms with the inevitable death of MLD patients.[5]

There is currently no curative treatment for MLD. Available treatments only address the symptoms of the disease and none of them have proven to reverse the fatal outcome.[3]

Clinical experts consulted by SMC considered that there is an unmet need in this therapeutic area for satisfactory treatments of the disease, as there are currently only supportive therapies.

1.3. Category for decision-making process

Eligibility for a PACE meeting

Atidarsagene autotemcel meets SMC ultra-orphan criteria for this indication.

2. Impact of new technology

Comparative efficacy

In the initial assessment of atidarsagene autotemcel for this indication (SMC2413), the following evidence was presented:

- Combined evidence from Study 201222 (phase I/II study) plus three early access programmes, which was naively compared with a natural history cohort.
- Supportive evidence from Study 205756 (single-arm study, cryopreserved/commercial formulation)

In this reassessment of atidarsagene autotemcel, additional evidence was provided:

- Study OTL-200-10, an ongoing observational study with two groups:
    - Group 1. Included patients from Study 201222, three early access programmes, and Study 205756 and naively compared with a natural history cohort. Group 1 had a larger sample size and longer follow-up than the original combined evidence. The natural history cohort group was also larger. These data inform the economic base case.
    - Group 2. Included patients outside of the clinical development programme (that is, patients treated for compassionate use after June 2020 in the framework of San Raffael-Telethon Institute for Gene Therapy [SR-TIGET] or treated in a real-world setting). These data inform economic scenario analyses.

Details of Study OTL-200-10 are presented in Table 2.1.

Table 2.1 Overview of relevant study[1, 3, 6]

Criteria	Study OTL-200-10
Study design	Ongoing, observational study. Includes evidence from: • Study 201222: open-label, single-arm, single-centre, phase I/II study. • EAPs: CUP207394, CUP206258 and hospital exemption HE205029 • Study 205756: open-label, single-arm study.
Eligible patients	To be eligible for OTL-200-10, patients had to have been treated with atidarsagene autotemcel in one of the clinical development programme studies or EAPs. Study 201222 recruited patients with pre-symptomatic late infantile MLD, pre-symptomatic early juvenile MLD, and early symptomatic early juvenile MLD, confirmed by ARSA enzymatic activity and genetic analysis. EAPs had similar eligibility criteria to Study 201222. Study 205765 recruited pre-symptomatic patients with early-onset MLD only (that is, late infantile, early juvenile, or an intermediate variant in between).
Treatments	Patients received atidarsagene autotemcel at doses ranging from 2 to 30 x 10^6 $CD34^+$ cells/kg, dependent on the yield of cells following manufacturing. Patients received a busulfan conditioning regimen prior to administration of atidarsagene autotemcel. Group 1 patients received the fresh formulation of atidarsagene autotemcel or the commercially available cryopreserved formulation. In Group 2, all patients were treated with the cryopreserved formulation.
Randomisation	Not applicable.
Efficacy outcomes	Select efficacy outcomes include total GMFM-88 score, ARSA activity measured in PBMC, development quotient, performance and verbal IQ, and overall survival.
Statistical analysis	Efficacy analyses were presented for Group 1. A small number of patients were excluded from the analyses as they did not fall within the approved indication for atidarsagene autotemcel.

Abbreviations: ARSA = arylsulfatase A; EAP = early access programme; GMFM = gross motor function measure; IQ = intelligence quotient; MLD = metachromatic leukodystrophy; PBMC = peripheral blood mononuclear cells.

In combined data from phase I/II studies and three early access programmes, atidarsagene autotemcel increased gross motor function scores in pre-symptomatic late infantile and in pre- and early symptomatic early juvenile MLD patients, when compared with a natural history cohort of MLD patients. Select efficacy outcomes from the initial ultra-orphan assessment are summarised in Table 2.2.

Table 2.2. Select key efficacy results for atidarsagene autotemcel[1, 3, 6]

	Initial UO assessment		UO reassessment	
	Atidarsagene autotemcel (n=29)[A]	**Natural history cohort (n=31)**	**Atidarsagene autotemcel (n=35) [B]**	**Natural history cohort (n=43)**
Median length of follow-up				
PSLI	2.98 years	-	7.10 years	-
PSEJ	2.99 years	-	4.03 years	-
ESEJ	3.97 years	-	9.99 years	-
Motor function - Total GMFM-88 score after treatment (adjusted mean)				
Subgroup	Year 2		Year 3	
PSLI	80% (n=10)	8.4% (n=8)	86% (n=17)	4.0% (n=9)

Mean treatment difference	71% (95% CI: 60% to 82%)				82% (95% CI: 74% to 90%)			
PSEJ	97% (n=4)	44% (n=8)			95% (n=10)		46% (n=11)	
Mean treatment difference	52% (95% CI: 25% to 80%)				50% (95% CI: 27% to 73%)			
ESEJ	74% (n=5)	30% (n=10)			70% (n=5)		26% (n=10)	
Mean treatment difference	44% (95% CI: 6.0% to 83%)				44% (95% CI: 4.1% to 84%)			
ARSA activity in total PBMC (adjusted mean; nmol/mg/h)								
Subgroup	Baseline	Year 2	Baseline	Year 2	Baseline	Year 3	Baseline	Year 3
PSLI	26.3 (n=14)	632.4 (n=9)	-	-	CIC	CIC	-	-
PSEJ	26.3 (n=5)	232.5 (n=4)	-	-	CIC	CIC	-	-
ESEJ	26.3 (n=5)	101.8 (n=4)	-	-	CIC	CIC	-	-
Note: normal range of ARSA enzyme activity is 30.56 to 198.02 nmol/mg/h								
Cognitive function – development quotient (adjusted mean score)								
Subgroup	Year 2				-		-	
PSLI	95.0 (n=8)	21.0 (n=4)			-		-	
PSEJ	107.7 (n=4)	32.2 (n=7)			-		-	
ESEJ	105.2 (n=5)	28.0 (n=10)			-		-	
Cognitive function – performance and verbal IQ								
Subgroup	-	-			Year 5			
PSLI	-	-			Performance IQ: 90% normal Verbal IQ: 70% normal (n=10) and 20% mild impairment		Performance IQ: 100% severe impairment Verbal IQ: 100% severe impairment	
PSEJ	-	-			Performance IQ: 100% normal Verbal IQ: 100% normal (n=1)		Performance IQ: 100% severe impairment Verbal IQ: 100% severe impairment	
ESEJ	-	-			Performance IQ: 67% normal and 33% mild impairment Verbal IQ: 67% normal and 33% moderate impairment (n=3)		Performance IQ: 100% severe impairment Verbal IQ: 100% severe impairment	
Note: normal cognition defined as IQ scores ≥85; severe impairment ≤55.								
Overall survival[C]								
PSLI	Alive at age 6 years:	Alive at age 6 years: 71% (n=19)			Alive at 13 years:		Alive at 13 years: 20% (n=31)	

	100% (n=15)		100% (n=19)	
PSEJ	Alive at age 9 years: 80% (n=5)	Alive at age 9 years: 100%(n=12)	Alive at 11 years: 91% (n=11)	Alive at 11 years: 80% (n=19)
ESEJ	Alive at age 11 years: 100% (n=5)	Alive at age 11 years: 76% (n=12)	Alive at 11 years: 100% (n=5)	Alive at 11 years: 80% (n=19)

[A] = Integrated data set. Included patients from Study 201222 and three early access programmes.
[B] = Group 1 of Study OTL-200-10. Included patients from Study 201222, three early access programmes, and Study 205756.
[C] = KM estimates
Abbreviations: ARSA = Arylsulfatase A; ESEJ = early symptomatic early juvenile; GMFM = Gross Motor Function Measure; IQ = Intelligence quotient; PBMC = Peripheral Blood Mononuclear Cells; PSEJ = pre-symptomatic early juvenile; PSLI = pre-symptomatic late infantile; UO = ultra-orphan.

*Efficacy results to support the ultra-orphan reassessment were considered confidential by the company**

Treatment with atidarsagene autotemcel also led to benefits in achieving development milestones, such as the 3-word sentence milestone, being able to stand independently and being able to walk independently.[6]

The submitting company also presented results from Group 2 of Study OTL-200-10. These data were used in an economic scenario analysis. Early indications suggest the results in Group 2 are broadly similar to those of Group 1.[6]

*Other data were also assessed but remain confidential.**

Comparative safety

Evidence to support the safety of atidarsagene autotemcel comes from the full analysis set (FAS) of Study OTL-200-10 (Group 1 and 2). No comparative safety data are available.

For the total follow-up post-atidarsagene autotemcel from Study OTL-200-10, 98% had any adverse event (AE). Common AEs occurring in >25% of patients (in the FAS) in the total follow-up post-atidarsagene autotemcel phase included febrile neutropenia , stomatitis, upper respiratory tract infection, blood immunoglobulin E (IgE) increased, gait disturbance, and gastroenteritis.[6]

Overall, atidarsagene autotemcel appears well tolerated. No treatment related serious AEs or deaths have been reported, and the safety findings are as expected for a haematopoietic stem cell transplantation therapy preceded by a myeloablative conditioning regimen.[3] The safety data presented in Study OTL-200-10 are consistent with data presented at the time of the initial assessment. Patients should be monitored for infection and hypersensitivity/infusion-related reactions following administration of atidarsagene autotemcel. Thyroid function, signs and symptoms of cytopenia, and anti-ARSA antibodies should also be monitored. See SPC for more details.[1]

*Other data were also assessed but remain confidential.**

Clinical effectiveness issues

The key strengths and uncertainties of the clinical case are summarised below.

Key strengths:

- Atidarsagene autotemcel is the first and only approved treatment for patients with pre-symptomatic late infantile, pre-symptomatic early juvenile, and early symptomatic early juvenile MLD.
- Treatment with atidarsagene autotemcel has been shown to increase ARSA enzyme activity, the deficiency of which is a key component of the MLD disease pathophysiology.[3] In Study OTL-200-10, ARSA activity in total peripheral blood mononuclear cells remained stable within or above the reference range throughout the duration of follow-up in 17 of 19 treated pre-symptomatic late infantile (PSLI) patients, all treated PSEJ patients (n=11) and all treated ESEJ patients (n=5).[6]
- Patients with pre-symptomatic disease (late infantile and early juvenile) MLD who received treatment with atidarsagene autotemcel had motor function and cognitive function within the normal range of healthy people[3], as evidenced by the outcomes such as total Gross Motor Function Measure (GMFM)-88 scores and performance and verbal IQ scores. In patients with early symptomatic early juvenile MLD the treatment effect was more variable. However, most patients had preserved mobility, cognition and communication, and the rate of decline is potentially slower compared with untreated patients.[3, 7] These results are clinically meaningful.[3]

Key uncertainties:

- Key data to support the efficacy and safety of atidarsagene autotemcel come from single-arm, open-label studies and early access programmes, which are prone to various biases which may affect interpretation of results. Randomised controlled studies are not feasible in this rare condition. The number of patients who have received treatment with atidarsagene autotemcel is limited as may be expected for such a rare condition. Atidarsagene autotemcel data were naively compared with data from a natural history cohort (in which data were prospectively and retrospectively collected) of MLD patients. There may be meaningful measured and unmeasured differences between these populations, including that the natural history cohort were not eligible for atidarsagene autotemcel treatment, as they were too symptomatically advanced at the time of the study enrolment. Due to the clinical and methodological differences between the patients and data compared there is some uncertainty associated with this comparison. The exact magnitude of benefit with atidarsagene autotemcel over standard of care is less certain, however it is likely sizeable.
- Based on the study results, the patients who derive most benefit from atidarsagene autotemcel are pre-symptomatic patients (late infantile or early juvenile). In current real-world settings, most patients with early-onset MLD are ineligible for treatment

with atidarsagene autotemcel by the time diagnosis is made.[7] Pre-symptomatic patients are only identified if there is an affected sibling, and the majority of new MLD patients will be symptomatic.[3] Consequently, the benefits of atidarsagene autotemcel may be less pronounced in Scottish clinical practice than observed in Study OTL-200-10.

- Longer-term data were submitted for this reassessment, ranging from 4 to 10 years across the subgroups. However, some uncertainty remains about maintenance of effects and long-term safety (important potential risks include the development of malignancies).

*Other data were also assessed but remain confidential.**

Clinical expert input:

Clinical experts consulted by SMC considered that atidarsagene autotemcel is a therapeutic advancement, as it is the first treatment available to target the underlying pathophysiology of the disease. They emphasised the importance of early diagnosis in order for patients to achieve maximal benefit from treatment.

3. Impact beyond direct health benefits and on specialist services

Given the potential of atidarsagene autotemcel to prevent onset of disease symptoms or slow down disease progression, it is anticipated that patients would be able to develop similarly to other children, participate in daily activities of living (for example walking, self-feeding) and education, and build and maintain social relationships. In addition, the potentially reduced reliance on symptomatic treatments and carer support would lead to potential cost savings to the health system and carers. Loss of family income and out-of-pocket costs could be reduced. However, the extremely high upfront acquisition cost for this single-dose treatment is likely to have significant service implications and is associated with financial risk to the service if the long-term predicted clinical benefits do not materialise. Clinical experts consulted by SMC considered that facilities for stem cell harvest and transfusion, time in hospital for peripheral stem cell collection or bone marrow aspiration, and marrow conditioning will be needed, which is not the case with supportive treatments currently used in this setting. In addition, in practice, patient identification could be an issue as it is not clear how presymptomatic MLD patients, with no symptomatic sibling already diagnosed with MLD, could be identified for treatment. Clinical experts consulted by SMC noted that newborn screening programmes may need to be implemented.

4. Patient and clinician engagement (PACE)

A patient and clinician engagement (PACE) meeting with patient group representatives and clinical specialists was held to consider the added value of atidarsagene autotemcel, as an orphan medicine, in the context of treatments currently available in NHSScotland.

The key points expressed by the group were:

- Metachromatic leukodystrophy (MLD) is a rare, genetic multisystem neurodegenerative disease, characterised by rapidly progressive loss of mobility, speech, swallowing, sight, hearing and cognition, leading to severe disability, dependence and early death, in childhood. Patients may develop epilepsy, become doubly incontinent, suffer pain, have gastrointestinal symptoms and complications in other organ systems. Symptoms are often difficult to manage effectively due to the rapidly progressing nature of MLD. Developmental milestones are progressively lost as their capabilities decline. They become increasingly isolated and their participation in life relentlessly diminishes as they lose their mobility, fine motor skills, sight and hearing.
- Patients with MLD need huge amounts of support from parents and extended family, and from hospices. The patient's home needs to be adapted. Parents provide round-the clock care and organise many healthcare interventions, such as medicines, prescriptions, physiotherapy, frequent healthcare appointments, and emergency admissions. Parents of children with MLD often give up work, which may lead to financial difficulties, and many suffer from fatigue and physical pain.
- The emotional impact on parents of watching their children's health deteriorate in this relentlessly cruel disease and the anticipatory grief of their death is immeasurable. The strain on parents and extended family is huge, with many experiencing fatigue, physical pain, anxiety, depression, isolation, anger and guilt. The nature of the condition and the death have a profound and lasting psychological impact on all the family for many years, with some reporting post-traumatic stress disorder and many requiring counselling. PACE participants explained that the strain of the condition can lead to addiction, divorce and loss of friends.
- The impact of MLD on siblings of the affected child is immense. Their parents have less time to care for them during their formative years, and they may struggle with anxiety, guilt and grief. They often need counselling and additional support.
- Atidarsagene autotemcel is the only disease-modifying therapy for MLD. It prevents the irreversible deterioration in health associated with MLD and restores patients to normal wellbeing, enabling them to reach developmental milestones, attend education and socialise, and have a normal life expectancy where they can plan for the future and contribute to society. There is a paradigm shift in the outlook for patients given atidarsagene autotemcel before symptoms appear compared to those who do not receive it, often described as night and day. It was also noted that even for children with early symptoms, atidarsagene autotemcel has huge benefits, as it stops the progression of the disease and the patient can live a full life.
- Atidarsagene autotemcel can transform the lives of the patient's family and carers. By restoring the patient to normal health and life expectancy it completely removes the substantial caring responsibilities and the physical, practical and emotional impacts that accompany an MLD diagnosis. They would be able to return to work, improving their

financial situation and contributing to society. Siblings would have a more normal life, enjoying usual childhood and family activities. There is a stark difference in the life of families when atidarsagene autotemcel treatment is given in time to be effective compared with those who receive a diagnosis too late.

- Clinical experts advise that it should be used in accordance with its product licence. The pre-treatment conditioning regimen is intense and travel to specialist centres can have a substantial impact on the patient and their family. However, all families are happy to endure these to obtain the remarkable benefits for the patient. It was noted that European best practice guidelines now give clearer information about the treatment journey, which is shorter and associated with less severe side-effects, with a clear follow-up plan to give reassurance that treatment is working.
- There is currently no routine newborn screening available for MLD. Clinical experts advise that identifying this metabolic disease early is key to obtaining benefits with this treatment. Efforts are being made to educate NHS staff to recognise early symptoms and to advocate for newborn screening. It was noted that without newborn screening, access for late infantile MLD is impossible. It was highlighted that turnaround testing for ARSA in Scotland (typical weeks) is slower than other parts of the UK.

Additional Patient and Carer Involvement

We received a joint patient group submission from The MPS Society, ArchAngel MLD Trust and MLD Support Association UK and a patient group submission from Alex, The Leukodystrophy Charity (Alex TLC). The MPS Society, ArchAngel MLD Trust and Alex TLC are registered charities. MLD Support Association UK is a charitable incorporated organisation. The MPS Society has received 14.5% pharmaceutical company funding in the past two years, including from the submitting company, ArchAngel MLD Trust has not received any pharmaceutical company funding in the past two years. MLD Support Association UK has received 49% pharmaceutical company funding in the past two years, including from the submitting company. Alex TLC has received 6% pharmaceutical company funding in the past two years, including from the submitting company. Representatives from all four organisations participated in the PACE meeting. The key points of their submissions have been included in the full PACE statement considered by SMC.

5. Value for money

5.1. Economic case

A summary of the economic analysis provided by the submitting company is outlined in table 5.1.

Table 5.1 Description of economic analysis

<table>
<tr><th>Criteria</th><th>Overview</th></tr>
<tr><td>Analysis type</td><td>Cost-utility analysis</td></tr>
<tr><td>Time horizon</td><td>Lifetime time horizon</td></tr>
<tr><td>Population</td><td>Patients with metachromatic leukodystrophy (MLD) characterised by biallelic mutations in the arylsulfatase A (ARSA) gene leading to a reduction of ARSA enzymatic activity:
• in children with Late Infantile (LI) or Early Juvenile (EJ) forms, without clinical manifestations of the disease,
• in children with the EJ form, with early clinical manifestations of the disease, who still have the ability to walk independently and before the onset of cognitive decline.</td></tr>
<tr><td>Comparators</td><td>Best supportive care (BSC) consisting of current available supportive therapies recommended by the international GLIA guidance.</td></tr>
<tr><td>Model description</td><td>The submitting company presented a partitioned survival model. The model had eight health states;
• GMFC-MLD = 0 (consistent with normal development for age)
• GMFC-MLD = 1 (reduced quality walking)
• GMFC-MLD = 2 (walking with support only)
• GMFC-MLD = 3 (loss of ambulation)
• GMFC-MLD = 4 (further motor loss)
• GMFC-MLD = 5 (no locomotion or sitting)
• GMFC-MLD = 6 (complete loss of motor function)
• Death
Patients entered the model aged based on the sub-group as presented in the table below
<table>
<tr><th>Disease Variant</th><th>GMFC-MLD Stage at Model Entry</th><th>Patient Age at Model Entry</th></tr>
<tr><td>PSLI</td><td>100% GMFC-MLD 0</td><td>18 months</td></tr>
<tr><td>PSEJ</td><td>100% GMFC-MLD 0</td><td>45 months</td></tr>
<tr><td>ESEJ</td><td>Commercial in confidence</td><td>80 months</td></tr>
</table>
Patients could not move back to earlier health state once transitioned, and all MLD-related deaths happened from the GMFC-MLD = 6 health state. For each of the GMFC-MLD stages in EJ patients, three cognitive sub-states were also included within each GMFC-MLD health state, to reflect the cognitive progression of MLD and capture the combined effects of cognitive decline and motor function loss on these patients.</td></tr>
<tr><td>Clinical data</td><td>Clinical data in the economic evaluation came from Group 1 in Study OTL-200-10 and a naïve comparison with the OSR-TIGET natural history (NHx) study. Compared with the initial assessment, the economic evaluation included longer follow-up data.</td></tr>
<tr><td>Extrapolation</td><td>The patients were split into different responder categories; full responder, stable partial responder and unstable partial responder. For the full responders a time to progression was set to the full time horizon assuming no treatment waning. The stable partial responder patients would progress then stabilise and stay in that stabilised state for the remainder of the time horizon. The unstable partial responders continued to experience deterioration despite the treatment but at a slower rate than patients in the comparator arm.
Atidarsagene autotemcel time to transitions were calculated by multiplying the 'progression</td></tr>
</table>

	modifier' value by the NHx time to transition for each GMFC-MLD stage. This involved deriving a ratio comparing the average time from GMFC-MLD stage 2 to GMFC-MLD stage 5 from the NHx study and atidarsagene autotemcel. These progression modifiers were applied to all GMFC-MLD transitions except the transition from GMFC-MLD stage 6 to death. Overall survival to calculate transition from GMFC-MLD = 6 to death was extrapolated using parametric curves and applying the Weibull distribution.
Quality of life	The submitting company utilised a vignette study in order to elicit HRQoL data. The vignette study was divided into two parts: a) Development of health state descriptions or vignettes using a literature review and qualitative clinical interviews. b) The valuation of the health states using the time trade-off (TTO) method. Carer disutilities were also incorporated and presented as sensitivity analysis.
Costs and resource use	Medicine costs included were acquisition costs and administration costs. Other costs were monthly MLD-related medical costs.
PAS	A Patient Access Scheme (PAS) was submitted by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHSScotland. Under the PAS, a complex PAS discount is offered on the list price of the medicine.

5.2. Results

SMC would wish to present the with-PAS cost-effectiveness results that were used for decision-making. However, SMC is unable to publish these results due to commercial in confidence concerns regarding the PAS.

*Other data were also assessed but remain confidential.**

5.3. Sensitivity analyses

A range of sensitivity and scenario analyses were considered and descriptions of these key scenarios are provided in table 5.2.

Table 5.2 Scenario analysis

	Parameter	**Base case**	**Scenario**
1	Discount rate (including caregiver disutilities)	3.5%	0%
2			6%
3	Progression modifiers	Clinical trial data	SEE data
4	Utility values	Original	Alternative value set (rescaled)
5	Distribution of MLD variants for the combined ICER	PS LI: 65.9% PS EJ: 19.2% ES EJ: 14.9%	PS LI: 29.5% PS EJ: 39.5% ES EJ: 31.0%
6	Natural history source data	OSR-TIGET	Elgun et al. (2019)

7			Kehrer et al. (2011)
8	Carer disutilities	Not included	Included
9	Partial responders stabilised	Lifetime	8 years
10	Full responders stabilised	Lifetime	15 years
11	Time horizon	Lifetime	30 years
12			40 years
13			50 years

Abbreviations: BSC = best supportive care; Incr. = Incremental; ICER =incremental cost-effectiveness ratio; QALY = quality-adjusted life year; MLD = metachromatic leukodystrophy; SEE = structured expert elicitation; PS LI = Pre-symptomatic late infantile; PS EJ = Pre-symptomatic early juvenile; ES EJ = Early symptomatic early juvenile; SEE= structured expert elicitation

5.4. Key strengths:

- The model type is appropriate for MLD.
- The submitting company provided updated clinical data on the efficacy of atidarsagene autotemcel making outcomes more robust than in the original submission which have provided reassuring efficacy results due to a larger sample size and a longer duration of follow-up

5.5. Key uncertainties:

- Atidarsagene autotemcel data were naively compared with data from a natural history cohort (in which data were prospectively and retrospectively collected) of MLD patients. There may be meaningful measured and unmeasured differences between these populations, including that natural history cohort were not eligible for atidarsagene autotemcel treatment, meaning that their disease profiles are inherently different. The exact magnitude of benefit with atidarsagene autotemcel over standard of care is less certain, however it is likely sizeable.
- The assumption that patients classified as full or partial responders will experience maintenance of their treatment effect for the duration of the model time horizon may overstate the benefits of atidarsagene autotemcel given that longer-term data are not available and the patient cohort is small. Sensitivity analysis was provided to explore the impact of using more conservative assumptions about ongoing benefits in the model (table 5.2 scenarios 9-13).
- It is unclear how to reliably diagnose patients with early juvenile MLD prior to onset of symptoms in families where an affected sibling is not already known to have the

condition. Earlier diagnosis of eligible patients remains an important consideration in order to maximise the available health gains from treatment.

- Use of a vignette study to estimate health state utility values is not aligned with SMC's preferred approach of using EQ-5D data to estimate such values. The impact of moving towards SMC's preferred approach by re-scaling utility values to fit the range in the EQ-5D UK value set increased the ICER (table 5.2 scenario 4); however, given the rarity of this disease, and known issues around getting young children to accurately complete EQ-5D questionnaires, the company's use of a vignette study may be appropriate and is consistent with submissions for other rare diseases seen by SMC.

6. Conclusions

The Committee considered the benefits of atidarsagene autotemcel in the context of the SMC decision modifiers that can be applied when encountering high cost-effectiveness ratios and agreed that as atidarsagene autotemcel is an ultra-orphan medicine, SMC can accept greater uncertainty in the economic case.

After considering all the available evidence and the output from the PACE process, the Committee accepted atidarsagene autotemcel for use in NHSScotland.

7. Costs to NHS and Personal Social Services

The company estimated there would be 2 patients eligible for treatment with atidarsagene autotemcel over the three years, 1 in year 1, 0 in year 2 and 1 in year 3. The uptake rate was estimated to be 100% in year 1 and 100% in year 3. This resulted in 1 patient estimated to receive treatment in year 1 and 1 patient in year 3.

SMC is unable to publish the with PAS budget impact due to commercial in confidence issues. A budget impact template is provided in confidence to NHS health boards to enable them to estimate the predicted budget with the PAS. This template does not incorporate any PAS discounts associated with comparator medicines or PAS associated with medicines used in a combination regimen.

*Other data were also assessed but remain confidential.**

8. Guidelines and protocols

There are currently no Scottish Intercollegiate Guidelines Network (SIGN), NICE or other national guidelines for the treatment and management of MLD.

The Global Leukodystrophy Initiative (GLIA) consortium has published in 2015 and updated in 2017 guidelines on the preventive and symptomatic care of patients with leukodystrophies (including MLD).[5, 10]

9. Additional information

9.1. Product availability date

28 February 2021

Table 8.1 List price of medicine under review

Medicine	Dose Regimen	Cost per course (£)
Atidarsagene autotemcel	**Atidarsagene autotemcel 3 to 30 x 10^6 $CD34^+$ cells/kg of body weight (at the time of infusion) intravenous infusion once.**	**£2,875,000**

Costs from electronic Dictionary of Medicines and Devices browser (DM+D) on 27 May 2026. Costs do not take any patient access schemes into consideration.

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This assessment is based on data submitted by the applicant company up to and including 15 June 2026.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal:*https://www.scottishmedicines.org.uk/about-us/policies-publications/

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC includes Scottish national contract prices in its decision-making. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document.

Patient Access Schemes (PAS): A PAS is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a medicine and enable patients to receive access to

cost-effective innovative medicines. The Patient Access Scheme Assessment Group (PASAG), established under the auspices of Public Services Delivery Scotland, reviews and advises NHS Scotland on the feasibility and acceptability on implementing proposed schemes. PASAG operates separately from SMC to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHS Scotland on the basis of a PAS that has been considered acceptable for implementation by PASAG, a set of guidance notes on the operation of the scheme will be circulated to health boards' Area Drugs and Therapeutics Committees prior to publication of SMC advice.

Assessment report context:

No part of the assessment summary on page one may be used without the whole of the summary being quoted in full.

This assessment represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.