atidarsagene autotemcel 2 to 10 x 10^6 cells/mL dispersion for infusion (Libmeldy®)

Orchard Therapeutics Limited

04 March 2022

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

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.

Key points:

- MLD is a condition that affects the nervous system resulting in multiple incapacitating symptoms including loss of motor and cognitive functions and early death, especially in patients with early disease onset. The caring burden impacts on the whole family.
- In combined data from a phase I/II study and three expanded access programs, 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. Survival data in late infantile patients treated with atidarsagene autotemcel are encouraging.
- Quality of life outcomes were not directly assessed in the studies.
- The sample size and follow-up were limited. Maintenance of effects and long-term safety are uncertain. In early symptomatic patients, treatment effect was less evident and more varied than in the pre symptomatic patients.
- Despite a Patient Access Scheme (PAS), the treatment's cost in relation to its health benefits remains high.

Chairman
Scottish Medicines Consortium

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Indication

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.[1]

Dosing Information

Atidarsagene autotemcel dose is based on the patient's weight at the time of infusion. The minimum recommended dose of atidarsagene autotemcel is 3×10^6 CD34+ cells/kg. In clinical studies, doses up to 30×10^6 CD34+ cells/kg have been administered. The maximum volume of atidarsagene autotemcel to be administered should remain <20% of the patient's estimated plasma volume.

Atidarsagene autotemcel is for autologous use and should only be administered once, as an intravenous (IV) infusion via a central venous catheter.

A myeloablative conditioning is required before infusion of atidarsagene autotemcel to promote efficient engraftment of the genetically modified autologous CD34+ cells. Busulfan is the recommended conditioning medicinal product.

Atidarsagene autotemcel must be administered in a qualified treatment centre with experience in Haematopoietic Stem Cell Transplantation (HSCT).

Patients are expected to be enrolled and be followed-up in a long-term follow-up study in order to better understand the long-term safety and efficacy of atidarsagene autotemcel.

See Summary of product characteristics (SPC) for further information. [1]

Product availability date

07 February 2022

SMC ultra-orphan designation

Atidarsagene autotemcel has been validated as meeting SMC ultra-orphan criteria:

- The prevalence of metachromatic leukodystrophy (MLD) is less than 1 in 50,000 of the population in Scotland.
- Atidarsagene autotemcel was awarded GB orphan designation for the treatment of MLD at the time of Marketing Authorisation (PLGB 49055/0002/OD1).

- MLD is a hereditary disease that is chronically debilitating and life threatening. The nervous system is progressively damaged resulting in loss of motor and cognitive functions and early death, especially in patients with early disease onset.
- MLD is a condition that requires highly specialised management.

Background

Atidarsagene autotemcel is an ex vivo genetically modified autologous CD34+ hematopoietic stem and progenitor cell (HSPC) gene therapy. Autologous CD34+ HSPCs are collected from patient bone marrow (BM) harvest or from mobilised peripheral blood (mPB). The cells are transduced with a lentiviral vector (ARSA LVV), which inserts one or more copies of the human ARSA complementary deoxyribonucleic acid (cDNA) into the cell's genome. The genetically modified cells become capable of expressing the functional ARSA enzyme. Administered following a myeloablative conditioning regimen, the genetically modified cells engraft and repopulate the haematopoietic compartment. A subpopulation of the infused HSPCs and/or their myeloid progeny is able to migrate across the blood brain barrier and engraft as central nervous system (CNS) resident microglia and perivascular CNS macrophages as well as endoneural macrophages in the peripheral nervous system (PNS). These can produce and secrete the functional ARSA enzyme, which can be taken up by surrounding cells (cross-correction) and used to break down, or prevent the build-up, of harmful sulfatides. Following successful and stable engraftment in the patient, the effects are expected to be persistent.[1]

Nature of condition

MLD is an 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 CNS and Schwann cell myelin membrane in the PNS. ARSA enzyme deficiency results in sulfatide accumulation, which leads, in the nervous system, to microglial damage, progressive demyelination, neurodegeneration, and subsequent loss of motor and cognitive functions and early death, especially in patients with early disease onset.

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) are characterised by a generally slower and more variable initial disease progression.

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 decerebrate state and eventually an early death. [2] Retrospective analysis of MLD cases since 1921 showed that median survival for late infantile and juvenile patients was 2.7 and 9 years, respectively. [3]

The severe deterioration in the physical and cognitive condition of the patient has 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 affect 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.[4]

There is currently no curative treatment for MLD. Available treatments only address the symptoms of the disease and none of them has proven to reverse the fatal outcome. [2]

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

Impact of new technology

Comparative efficacy

Evidence to support the efficacy of atidarsagene autotemcel for the indication under review comes from an open-label, non-randomised, single-arm, single-centre, phase I/II study, Study 201222 (n=20), and three expanded access programs (EAPs) with a similar design (compassionate use programs CUP207394 [n=1] and CUP206258 [n=5] and hospital exemption HE205029 [n=3]).These were combined to form the Integrated Data Set (IDS; n=29). They included children with early-onset MLD, which is patients with late infantile or early juvenile variants. MLD diagnosis was based on ARSA enzymatic activity and genetic analysis. Patients' conditions were classed as pre- or early-symptomatic.[2] Pre-symptomatic patients, at inclusion, were without neurological impairment (disease-related symptoms), with or without signs of the disease revealed by instrumental evaluations. For early juvenile patients, early symptomatic status at inclusion was initially defined as within 6 months after the first reported symptom, but later with Intelligence Quotient (IQ) $\geq$70, ability to walk independently for $\geq$10 steps. Within the IDS, there were 16 patients with late infantile MLD (all but one were pre-symptomatic) and 13 with early juvenile MLD (5 pre-symptomatic and 8 early symptomatic).[1]

Across these studies, patients were to receive atidarsagene autotemcel fresh formulation at doses between 2 to 30 x 10^6 CD34+ cells/kg, following a conditioning regimen.[2] Patients received a mean cell dose of 10.81 x 10^6 CD34+ cells/kg (ranging from 4.2 to 25.9) as an intravenous infusion.[1]

The co-primary efficacy outcomes common to all the included studies were: [1, 2]

- Gross Motor Function Measure (GMFM) score: total GMFM score two years after treatment. Delay in progression of >10% in total of the total GMFM score in treated patients as compared to a concurrent historical control group was the aimed effect size. The GMFM instrument used consists of questions organised into domains (such as sitting, standing; and walking). Each question is scored (from 0 to 3) and the total score is expressed as a percentage of the maximum score, with 0% corresponding to loss of all voluntary movement.[5]
- ARSA activity in peripheral blood mononuclear cells (PBMC). A significant (≥2 standard deviation [SD]) increase in residual ARSA activity measured in the PBMC at two years as compared to pre-treatment values, was the aimed effect size.

Results were compared with a natural history cohort, which included untreated symptomatic early-onset MLD patients (n=31 [19 late infantile and 12 early juvenile]). Retrospective and prospective data were collected for this cohort to allow comparisons matched on age, variant and symptomatic status. [2]

At two years, total GMFM score was greater in patients treated with atidarsagene autotemcel compared with untreated natural history cohort patients, as detailed in Table 1 below. At two years, ARSA activity had increased in the total PBMCs of patients treated with atidarsagene autotemcel compared with baseline. The co-primary efficacy outcomes are summarised in Table 1. GMFM total score data at three years were supportive of a continuing effect of atidarsagene autotemcel, with an increasing score difference versus the natural history cohort relative to data at two years after treatment.[1]

Table 1. Co-primary efficacy outcomes results for the IDS versus the natural history cohort [1]

	IDS (n=29)		Natural history cohort (n=31)
Total GMFM score 2 years after treatment [a, b]			
Pre-symptomatic - Late infantile patients			
Adjusted mean	80% (n=10)		8.4% (n=8)
Mean treatment difference	71% (95% CI: 60% to 82%)		
Pre-symptomatic - Early juvenile patients			
Adjusted mean	97% (n=4)		44% (n=8)
Mean treatment difference	52% (95% CI: 25% to 80%)		
Early Symptomatic- Early juvenile patients			
Adjusted mean	61% (n=6)		32% (n=10)
Mean treatment difference	29% (95% CI: -14% to 72%)		
ARSA activity measured in the PBMC at 2 years as compared to pre-treatment values [b]			
	Baseline	**Year 2**	
Pre-symptomatic patients			
Geometric mean (%CVb)	26.923 (n=19)	339.736 (n=14)	N/A

Early symptomatic patients			
Geometric mean, (%CVb)	26.025 (n=9)	134.056 (n=6)	N/A

Abbreviations: CI: confidence interval; CVb: coefficient of variation between subjects; GMFM: gross motor function measurement; MLD: metachromatic leukodystrophy; PBMC; peripheral blood mononuclear cells, IDS, Integrated Data Set; N/A, not applicable.

Note:

[a] Comparisons between the IDS and natural history cohort were based on matching of data by age, variant and symptomatic status from patients with available relevant data (not all patients had two years data).

[b] All comparisons are descriptive only.

Relevant to the indication, the submitting company reported efficacy from a post-hoc analysis focused on patients within the IDS who fall within the approved indication (referred to as the Indicated Population [IP].[6] Results for the IP were consistent with the IDS results.

Secondary outcomes supportive of the clinical benefits of atidarsagene autotemcel included Intelligence Quotient/Development Quotient (IQ/DQ) and overall survival.

Out of the 16 late infantile patients treated with atidarsagene autotemcel, all but two (one pre-symptomatic, one early symptomatic) remained above the threshold of severe mental disability (IQ/DQ >55) at chronological ages, with 12 being within the normal range (IQ/DQ score of 100 +/- standard deviation of 15) throughout follow-up. All 14 untreated natural history cohort patients with neuropsychological assessments showed evidence of severe cognitive impairment (IQ/DQ <55 and close to 0). Of the 10 surviving early juvenile patients treated with atidarsagene autotemcel, the four pre-symptomatic patients and four out of six early symptomatic patients showed normal IQ/DQ throughout follow-up. Of the 12 natural history early juvenile cohort patients with neuropsychological assessments, 11 showed evidence of severe cognitive impairment during follow-up.[1]

At a median follow-up time of 3.04 years post-treatment (range 0.99 to 7.51), all 16 patients in the treated late infantile subgroup were alive. Twelve (63%) out of 19 untreated late infantile patients in the natural history cohort study, had died at the time of the analysis which would have been at a longer follow-up time that the treated group.[1] Comparable overall survival was observed in the treated and untreated early juvenile groups.[1]

Supportive evidence is derived from Study 205756, which is an open-label, single-arm study assessing the cryopreserved (commercial) formulation of atidarsagene autotemcel (at cell dose range 10.45-30.0 x 10^6 CD34+ cells/kg) in pre-symptomatic late infantile and pre-and early symptomatic early juvenile patients. Preliminary efficacy data from six pre-symptomatic patients (three late infantile, three early juvenile), with a median follow-up of 0.87 years (range 0 to 1.47 years) show that, at different timepoints, ARSA activity was within the range observed for the patients treated with the fresh formulation.[1]

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

Comparative safety

No comparative safety data are available. Refer to the SPC for details. [1]

Overall, although the safety data set is based on a limited number of patients (n=35) with a limited duration of follow up (median duration 4.51 years with fresh formulation), the safety of atidarsagene autotemcel was considered as expected for an autologous HSCT therapy preceded by myeloablative/submyeloblative conditioning regimen. Most of the adverse events (AEs) observed appeared related to the busulfan conditioning regimen. The AEs attributed to atidarsagene autotemcel was the presence of anti-ARSA antibodies, and this occurred infrequently and did not appear to impact efficacy.[2] The safety profile observed in Study 205756 using the cryopreserved formulation was consistent with the profile of the fresh formulation in terms of nature, time of onset and frequency of reported adverse events. [1]

Clinical effectiveness issues

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

Key strengths:

- The treatment effect in pre symptomatic patients enabled them to perform consistently within ranges reported for healthy subjects for motor and cognitive functions.[2]
- Survival data in late infantile patients are encouraging.

Key uncertainties:

- Accepting that MLD is a very rare condition, very few patients have been treated with atidarsagene autotemcel to date; and based on this small sample size, there may be some uncertainty regarding the statistical robustness of analyses and the magnitude of treatment effect within the described classifications.
- The mean duration of follow-up (IDS: 4.0 years for Study 201222, and 1.5 years for the three EAPs)[1] is limited for a gene therapy and uncertainty remains about maintenance of effects and long-term safety (important potential risks include the development of malignancies). To further characterise the long-term efficacy and safety of atidarsagene autotemcel in children with late infantile or early juvenile forms of MLD, the marketing authorisation holder will conduct and submit the results of a prospective study based on data from a registry.[2]
- The key supporting dataset included data combined (into the IDS) from non-identical, non-randomised, open-label, single-group studies to increase patient numbers included in the analysis. Data of this nature are prone to various biases. Each of the studies are being conducted at the same study centre by the same clinical team.

- 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, as they were too symptomatically advanced at the time of the enrolment in the studies.
- Confidence intervals of differences in GMFM total score between the IDS/IP and natural history cohort are wide, reflecting the uncertainty with this comparison.
- A large variability in treatment effect was noted across subpopulations with maintenance of GMFM scores/stabilisation in disease course seen in some patients and rapid deterioration in others.
- In early symptomatic patients, treatment effect was less evident and more varied than in the pre symptomatic patients.
    - One late infantile patient became symptomatic between inclusion in the trial and prior to receiving treatment. Unlike the pre-symptomatic late infantile patient that benefited from atidarsagene autotemcel treatment, this patient performed for all outcomes within ranges and close to the natural history cohort indicating that the window of opportunity to perceive treatment benefit on either motor function or cognitive function was missed. Therefore, treatment in late infantile should be initiated before patients become symptomatic.[2]
    - A significant deterioration of motor function was observed for treated patients with early symptomatic early juvenile MLD. Data suggest that this deterioration may be less rapid than in untreated patients, but this was considered uncertain based on available data. In the symptomatic early juvenile patients with IQ>85 and a Gross Motor Function Classification in MLD (GMFC-MLD) ≤1 (patient is able to walk independently), cognitive function appeared to be preserved indicating a window of opportunity for the early symptomatic early juvenile population. Treatment may be beneficial to preserve cognitive function, as well as halt or slow down the rate of deterioration. This cut-off to define early symptomatic status for early juvenile patients (IQ>85 and a GMFC-MLD ≤1) was accepted and is defined in the SPC; however, it may need to be adapted as more data become available.
- Quality of life outcomes were not directly assessed in the studies.
- The majority of data presented are from patients treated with the fresh formulation of atidarsagene autotemcel, therefore there is limited evidence available using the commercial cryopreserved formulation.

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.

The clinical case is considered reasonable in the short-term and the regulator mandated additional pharmacovigilance activities may help to address uncertainties associated with the longer term clinical case.

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 pre-symptomatic 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.

Patient and carer involvement

The following information reflects the views of the specified Patient Groups.

- We received a joint patient group submission from: The MPS Society, ArchAngel MLD Trust and MLD Support Association UK. The MPS Society and ArchAngel MLD Trust are both registered charities. MLD Support Association UK is a charitable incorporated organisation.

- In the past two years, The MPS Society has received 16% pharmaceutical company funding, ArchAngel MLD Trust has received 33% pharmaceutical company funding and MLD Support

Association UK has received 35% pharmaceutical company funding, all including from the submitting company.

- Patients with MLD endure multiple incapacitating symptoms, creating a significant burden to caregivers and resulting in wide-reaching repercussions across relationships, finances, physical and mental health. Children rapidly lose the ability to walk, talk, swallow, see, hear and become doubly incontinent; they develop serious muscular and skeletal complications, including scoliosis and hip dislocations; they go on to suffer epilepsy and dementia; and can endure a final protracted period of suffering in an unresponsive state.

- Palliative care/ best supportive care is the only current option for these patients. Care is challenging and time intensive. There is a need for multiple symptoms to be managed including: gastrointestinal issues, chest infections, secretions and suctioning, dystonia and spasticity.

- The patient groups reported that the experiences of untreated patients and those treated with atidarsagene are strikingly different. They said treatment allowed children to fully participate in everyday life and achieve an education. They described how, in over 33 patients world-wide who have received the treatment, it has had remarkable results, with many children still asymptomatic at the same age, or having surpassed the age, of when an elder untreated sibling had passed away.

- The burden on parents/carer and wider family of non-treated patients is all encompassing with many having to give up work, becoming full time carers, experiencing loss of income and financial hardship. The patient groups described that, in contrast the children on treatment are attending either mainstream or special educational needs schools full time and only attending routine follow up appointments with no hospital stays. They added that the carer burden is reduced to normal parameters when caring for a child in most cases.

- Regarding disadvantages, the patient groups noted that the side effects of chemotherapy before treatment were difficult for both patients and families.

Value for money

The company presented a cost-utility analysis assessing atidarsagene autotemcel versus best supportive care (BSC) for the treatment of MLD characterised by bi-allelic mutations in the ARSA gene leading to a reduction of ARSA enzymatic activity: in children with late infantile or early juvenile forms without clinical manifestations of the disease, or 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. BSC was defined as a combination of treatments provided to alleviate the burden of symptoms and included: physical therapy to

maintain mobility, muscle relaxant medications to reduce spasticity, pain management, management of skeletal deformity, respiratory physiotherapy to manage pulmonary infections, anticonvulsant medications to control seizures, anti-psychotic medications to control psychiatric symptoms, dietary support, enteral nutrition through a feeding tube in cases of dysphagia, and family and psychological counselling.

The economic model created by the company is a combination of a Markov model and a partitioned survival model (referred to as a 'semi-Markov model'); the model has 7 core health states (excluding death) that are aligned with the different stages of motor function loss outlined in the GMFC-MLD system. The company has assumed that it is not possible for patients to experience improvement in their motor function, and that it is only possible for patients to transition to the death state due to complications of MLD from GMFC-MLD stage 6. Death due to other causes could occur from any health state. For patients with early juvenile MLD, the model structure is expanded by dividing each GMFC-MLD health state into 3 sub-health states describing patients' level of cognitive function as measured by their developmental quotient (DQ): normal, cognitive impairment: DQ < 70, or severe cognitive impairment: DQ < 55. The company state that these additional sub-health states were not required for the late infantile MLD population, as cognitive decline occurs at a similar rate to motor function decline, and therefore can be accounted for by the GMFC-MLD health states alone.

The relative efficacy data source used in the economic evaluation for atidarsagene autotemcel was a post hoc analysis of the indicated population from an integrated dataset comprising a phase I/II, open-label, non-randomised, single-arm, single-centre study, two compassionate use programmes, and a hospital exemption programme.[6] The efficacy of BSC was estimated using data from the natural history study of patients at the Telethon Institute for Gene Therapy. Transition probabilities between adjacent health states were estimated using data on the mean time to progression from these studies, and overall survival was extrapolated over the model time horizon using the Weibull distribution based on a combination of statistical fit and clinical expert opinion.

Health state utility values were derived from a multi-stage vignette study commissioned by the company; in the initial stage, a series of health state descriptions were developed by combining information obtained from the published literature with insights from clinician interviews. Next, members of the UK general public were asked to indirectly attach utility values to the health states described using the time trade-off method. Caregiver disutility was also accounted for via scenario analyses. This was estimated via a postal survey created by the company where caregivers of patients with MLD were asked to complete an EQ-5D questionnaire, finding an average disutility impact per caregiver. Disutility due to adverse events was not included.

Medicine acquisition costs were included for atidarsagene autotemcel and BSC. Other costs associated with the administration of atidarsagene autotemcel were also included however the

costs of adverse events and wastage were not. Non-medicines healthcare costs (e.g. medical tests, emergency visits, inpatient stays) were accounted for and estimated by a group of healthcare professionals through a structured expert elicitation study.[7]

A patient access scheme (PAS) was submitted by the company and was assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHSScotland. Under the PAS, a discount is offered on the list price of atidarsagene autotemcel.

SMC would wish to present the cost-effectiveness estimates for atidarsagene autotemcel. However, owing to commercial in confidence concerns, SMC is unable to publish any results.

The main economic results at PAS price for atidarsagene autotemcel indicate that atidarsagene autotemcel is both more costly and more effective than BSC. Disaggregated analyses suggest that incremental quality-adjusted life-years associated with atidarsagene autotemcel stem from both an increase in life expectancy and improvements in quality of life. The majority of incremental costs associated with atidarsagene autotemcel are due to the acquisition costs of the treatment.

A number of scenario analyses were obtained during the assessment process. These highlight that the model is sensitive to the assumed distribution of patients by disease variant, alternate methods for analysing response status, and assumptions around the point at which treatment waning may or may not occur.

The following limitations of the economic evaluation were noted:

- Uncertainty around the magnitude of the treatment effect exists given the limited number of patients that have been treated with atidarsagene autotemcel so far. Scenario analysis provided demonstrates the impact of removing two patients with less than 2 years follow up from the calculation of clinical effectives parameters, finding an increase in the ICER.
- 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 maximum duration of follow-up across all studies is 8 years, with average durations significantly shorter. Scenario analyses explored the impact of assuming that patients experience treatment waning at different time points and indicate the potential for a significant increase in the ICER. The extremely high upfront costs add considerable uncertainty to the ICER, in the context of uncertain medium to long term outcomes, which might be mitigated by different payment models.
- 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. Given differences in cost-effectiveness by sub-group, if a larger proportion of early juvenile patients were to be diagnosed only once early symptoms had emerged than assumed in company's base case, this would increase the ICER significantly. Furthermore, the cost of

the national screening programme that would be required to diagnose these patients prior to symptom onset has not been accounted for in the company's base case results.

- 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, creating uncertainty when trying to compare the incremental QALYs associated with atidarsagene autotemcel with other submissions to SMC. The impact of moving towards SMC's preferred approach by re-scaling utility values to fit the range permitted by the EQ-5D measure increases the ICER; 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 recently.

The cost of atidarsagene autotemcel in relation to its health benefits remains high, and there are a number of outstanding uncertainties relating to the incremental clinical and patient benefits over the longer-term.

Costs to NHS and Personal Social Services

The submitting company estimates that there will be 1 patient eligible for treatment with atidarsagene autotemcel every two years over a year 1 to year 5 timeframe, with an uptake rate of 100% each year.

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.

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

Additional information: 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).[4,8] The recommendations included in this paper are based on existing studies and consensus opinions. The guidelines mention that for a minority of leukodystrophies, there are curative options, such as hematopoietic stem cell transplantation. However, for the majority of forms there are no curative options. Patients with leukodystrophies have a wide variety of issues, ranging from behavioural and sleeping difficulties, to requirements for assisted ventilation, to potential surgical interventions. A comprehensive approach that encompasses all relevant organ systems with involvement of a multidisciplinary team is recommended. This includes guidelines to manage the following key areas:

- Musculoskeletal issues: the focus is to maintain ambulation for bone health (reduce risk of low bone mass and hip issues) and emotional well-being. Spasticity can be managed with oral medications such as baclofen or diazepam in combination with physical therapy. Anticholinergic medication trihexyphenidyl is well tolerated to reduce dystonia. Spinal orthoses can maximise chest expansion with those with mild scoliosis. Bone health monitoring (vitamin D supplementation may be needed) and management of skeletal deformity are needed (surgery may be needed).
- Nutrition, bowel, and urinary tract issues: interventions to reduce drooling include oromotor or behavioural exercises, positioning as well as medications such as anticholinergic agents. Speech and occupational therapy can provide interventions such as positioning and adjustment of food consistency to help with swallowing problems, gastroesophageal reflux and feeding issues. Gastrostomy tubes are considered effective to deliver medications, prevent respiratory complications and thus reduce hospitalisations.
- Respiratory health and communication issues: managed by infection prevention (influenza vaccination) and airway maintenance (repositioning, ambulation and chest therapy). Comprehensive augmentative and alternative communication evaluation is used to meet the patients' individual communication needs.
- Neurologic issues: pain and seizures are key areas of concern and thorough investigation should try to identify the trigger. Gabapentin can be used to relive neuroirritability and neuropathic pain.
- Endocrine issues: Adrenal insufficiency can be treated with corticosteroid supplementation
- Psychosocial issues: Anti-psychotic medications to control psychiatric symptoms, and family and psychological counselling.

Additional information: comparators

Supportive treatments.

Additional information: List price of medicine under review

Medicine	Dose Regimen	Cost per patient
atidarsagene autotemcel	**Single IV infusion via a central venous catheter at a dose based on the patient's weight**	**£2,875,000**

Costs from company submission. 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 11 April 2022.

**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: http://www.scottishmedicines.org.uk/About_SMC/Policy*

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC assessment report.

Patient access schemes: A patient access scheme 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. A Patient Access Scheme Assessment Group (PASAG), established under the auspices of NHS National Services Scotland reviews and advises NHSScotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When a medicine is available through the ultra-orphan pathway, a set of guidance notes on the operation of the patient access scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC assessment report.

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.