



21345 Miles Drive
West Linn, OR 97068-2878

+1 503-656-4808
FAX: +1 503-446-2418

deansuhr@MLDfoundation.org

www.MLDfoundation.org

A registered 501(c)(3) non-profit serving families worldwide

March 30, 2023

Kelsey Gosselin, Program Manager
Institute for Clinical and Economic Review
14 Beacon Street
Boston, MA 02108


re: Comments on Draft Scoping Document – Atidarsagene Autotemcel for Metachromatic Leukodystrophy

Dear Ms. Gosselin,

MLD foundation is pleased to respond to ICER’s request for comments on the Draft Scoping Document for Atidarsagene Autotemcel for Metachromatic Leukodystrophy.

Pg 1 ¶2 ... Incidence & Prevalence ... “under 50,000 US patients” ... MLD Foundation analysis estimates approx. 2,500 patients alive with MLD in the USA at any given time. Newborn screening will refine these estimates. See below. We can provide our source assumptions that drive this summary.

MLD Incidence & Prevalence Domestic & Worldwide

|  | Incidence - Births | | | Prevalence - Alive | | |
|---|--------------------|--------------------------|--------------|--------------------|--------------------------|---------------|
| | USA | More Developed Countries | Global | USA | More Developed Countries | Global |
| Late Infantile | 70 | 179 | 1,876 | 490 | 1,250 | 13,129 |
| Juvenile | 32 | 81 | 853 | 636 | 1,623 | 17,051 |
| Adult | 48 | 65 | 682 | 1,324 | 3,377 | 35,466 |
| Total | 127 | 325 | 3,410 | 2,450 | 6,250 | 65,647 |

© 2017-2021 MLD Foundation, all rights reserved. Please credit source. * Data last updated Feb-2021
Please contact us for further details and assumptions. **More Developed Countries** as defined by the United Nations.

Pg 1 ¶2 ... Juvenile is being divided into early juvenile and late juvenile, primarily based on whether motor or cognitive skill loss occurs first. For example, Libmeldy targets late infantile and early juvenile patients. ICER makes this distinction later on in the Draft scoping Document.

Pg 1 ¶2 ... adult MLD is not "least" severe, it is just a bit slower in its progression – Adult MLD is also terminal.

Pg 2 ¶2 ... treatment ... respiratory therapy and related treatments are very common.

Pg 2 ¶2 ... In the absence of Newborn Screening Libmeldy access will also be limited due to patients being too far progressed at time of diagnosis.

Pg 2 ¶3 ... Libmeldy is not an "emerging" therapy. It was developed and is approved in the EU.

Pg 3 ¶2 ... As MLD progresses ... respiratory equipment including suction and breathing assists are often used to facilitate breathing and prevent pneumonia.

Pg 3 ¶3 ... MLD children often are either already on Medicaid, or due to the loss of parental income end up on Medicaid. Late infantile MLD is part of the SSI Compassionate Allowances (CAL) initiative. This initiative is a way to expedite SSI approval and the processing of SSDI and SSI disability claims. MLD patients often end up with county/state Disability Services support. So in addition to the increases in direct out of pocket expenses, MLD families also become a significant beneficiaries of a variety of governmental agencies and services.

Pg 3 Comparators ... HSCT should be a comparison in addition to usual care.

Pg 6 Outcomes ... patient verbal communication of feelings/desires and details of pain are very important to parents. Bowel, digestive, respiratory, tone and/or positional comfort are also key issues.

Pg 6 Outcomes ... In addition to caregiver burden, impact on other immediate family members (especially siblings), and financial burden on the family, their insurance, and public services & support should be considered.

Pg 6 Harms ... we support the use of the word harm, however, when it drifts into risk of harm the specific risk tolerance of MLD families for benefit vs. harm needs to be explicitly identified and included.

Pg 6 Harms ... families worry about preserving the life of a loved one whose progression is dramatically slowed but not halted. parents worry what happens to their disabled loved one when the primary caregiver (usually the parents) pass away?

Pg 6 ... Other outcomes ... parents are not implicitly concerned about these other scientific outcomes. Caution should be used when evaluating the impact of "Other outcomes" as there are often only gross correlations, not precision correlations to

therapeutic success or failure.

Pg 6 Outcomes ... it is fascinating that Patient Outcomes include harms, but do not explicitly (at least structurally in the document) identify benefits

Pg 7 Contextual Considerations ... the analysis should include equity, social, and economic impacts across the US population ... access to the proposed therapy, fundamental objections or concerns about the therapy, its administration, etc.

Sincerely,

A handwritten signature in black ink, appearing to read "Dean Suhr". The signature is fluid and cursive, with a large initial "D" and "S".

Dean Suhr, President
MLD Foundation

Orchard Therapeutics Response to the Draft Background and Scope for the Assessment of Atidarsagene Autotemcel (arsa-cel) for MLD

Orchard Therapeutics welcomes the opportunity to comment on the draft scoping document prepared by ICER in anticipation of the assessment of arsa-cel for the treatment of early onset MLD. As stated in the guide to manufacturers, comments within this document are focused on the following areas: 1) background, the appropriate population, interventions, comparators, outcomes, timeframe, and setting(s) of care (PICOTS) to be considered in the review, and 2) the economic analysis approach broadly described in the draft scope.

1 PICOTs

Background:

An important consideration to add to the background section is that early onset MLD is rapidly progressive. Fumagalli *et al*¹ showed that late-infantile (LI) and early-juvenile (EJ) subjects had similar rapid loss of ambulation and onset of seizures, but late-infantile displayed earlier loss of trunk control, dysphagia, and death. The median time from onset of symptoms to >GMFC-MLD 4 (defined as no ambulation and complete loss of trunk control) for LI and EJ patients was only 1.12 years and 2.7 years, respectively.¹ In addition, the median time to not being able to swallow was 0.88 years and 1.58 years.¹ Consequently, given that the median survival for LI patients was 8.42 years, and 68.6% of EJ patients were alive 15 years from symptom onset in the same study, this means that untreated early onset MLD patients spend the majority of the remainder of their lives with significant morbidity. This contributes to the extremely high caregiving burden already mentioned in the scope, but also has a significant impact on healthcare resource use.

Populations:

Orchard Therapeutics agrees with the defined population outlined on page 5 of the draft scope; however, it would like to add some additional clarity to the definition of early symptomatic early juvenile MLD that will help inform the specific population for this assessment of the clinical and cost effectiveness of arsa-cel. Early symptomatic early juvenile MLD patients who would benefit from treatment with arsa-cel are characterized as still being able to walk independently and who have not had any cognitive decline. This means that the patient's GMFC-MLD score should be ≤ 1 , and the patient's IQ should be ≥ 85 . The rationale for this definitive eligibility criteria is based on a post hoc analysis of baseline characteristics of all the patients treated in the clinical trial treated with arsa-cel and is also reflected in the licensed indication granted by the European Medicines Agency.

2 Scope of Comparative Value Analyses

Model structure:

Orchard Therapeutics broadly agrees with the structure of ICER's proposed economic model and considers health states grounded on the Gross Motor Function Classification-MLD to be a suitable framework for capturing the progressive nature of the disease. The company would like to emphasize that other aspects of the disease in addition to motor outcomes, such as cognition and ability to retain speech are important considerations in evaluating the health-related quality of life of MLD patients, given that MLD causes multi-system devastation.

Time Horizon:

Orchard Therapeutics also agrees that a lifetime horizon is appropriate based on the mechanism of action of arsa-cel as a transformative *ex-vivo* gene therapy. It also understands the need to assume different time horizons to test the impact these have on cost-effectiveness. However, an arbitrary 5-year time horizon seems to be very conservative and doesn't reflect the available clinical data for arsa-cel (up to 12 years of follow-up) or data from other hemopoietic stem cell-based therapies for analogous rare diseases e.g., Strimvelis, a hemopoietic stem cell gene therapy for adenosine deaminase severe combined immunodeficiency (ADA-SCID), or allogeneic HSCT for Hurler's syndrome (mucopolysaccharidosis type 1 [MPS1H]), which have shown 20 and 30 years, respectively, of maintained clinical response.²

For gene therapies like arsa-cel or Strimvelis, all the costs are up-front as they are one-time only treatments. Consequently, an arbitrary 5-year time horizon would unfairly penalise any treatment of this nature because

the cost of the treatment would be incurred but there would not be enough time to accrue the expected significant number of QALYs/LYs that gene therapies can offer, resulting in an incremental cost-effectiveness ratio vs. best supportive care greater than the \$100,000-\$150,000 per QALY gained threshold. With a 5-year time horizon, even if a perfect quality-of-life weight is assumed, the maximum number of QALYs that could be accrued in this period is only 5. This is in stark contrast to the UK health technology evaluation of arsa-cel, where NICE acknowledged incremental QALY gains for arsa-cel vs. best supportive care of greater than 30 QALYs.

Consequently, Orchard suggests for the sensitivity analyses of alternative time horizons that 20-, 30- and 50-year time horizons are more appropriate, which better reflect the available data and mechanism of action.

Caregiver disutility:

The scope states that “*the caregiving impact for the disease is very high*”, however it is unclear from the information in the scope whether the HRQoL of caregivers will be included in the proposed economic model. Pang *et al*³ investigated the quality of life of caregivers (n=21) of children with MLD, for whom the majority of the children had loss of trunk control (>GMFC 4), from the US, Germany and the UK. EQ-5D data were collected for the whole caregiver dataset (n=21), which resulted in a mean caregiver utility value of 0.773. As an example, the calculated general population utility (UK) at 40 years of age is 0.882 based on the method by Ara and Brazier⁴: $EQ-5D = 0.9345 + 0.0212126 * male - 0.0002587 * age - 0.0000332 * age^2$. This equates to a disutility of 0.108 for caregivers of patients with MLD. Given the acknowledged high burden of disease, the base-case analyses should include caregiver disutility when applying utility values to health states.

Based on the data from the caregiver survey, a caregiver disutility specific to the US could supplement the utility values assigned to health states from GMFC-MLD 4 onwards.

MLD phenotypes:

The scope states that the economic model will assess the lifetime cost-effectiveness of arsa-cel relative to usual care, which is appropriate. However, Orchard would like to highlight that there are three patient populations under review in this assessment – pre-symptomatic late infantile (PS-LI) MLD, pre-symptomatic early juvenile (PS-EJ) MLD and early symptomatic early juvenile (ES-EJ) MLD.

Patients treated pre-symptomatically and well in advance of predicted onset of symptoms have the potential to remain symptom free and lead a healthy, normal life accruing health gains similar to the general population. However, by nature of being symptomatic at baseline, ES-EJ patients will have some level of motor impairment at the point of treatment, and as gene therapy does not reverse symptoms, but rather halts or slows down the rate of further decline, these patients will continue to have some motor dysfunction that will persist throughout their lifetime e.g., a patient may need orthotics or require a wheelchair depending on the initial level of motor damage that occurs before or during the engraftment phase for arsa-cel. Consequently, the achievable health outcomes are different between the pre-symptomatic and early symptomatic MLD patients, which will need to be represented appropriately in the value assessment of arsa-cel.

In other health technology assessments, a pooled ICER for arsa-cel vs. BSC has been presented which reflects the epidemiology of the MLD variants in the country. For example, the incremental cost-effectiveness ratio is weighted according to the proportions of the patients displaying each of the different phenotypes e.g. 50-60% for LI. This same principle could be an option for this assessment.

Sensitivity analyses:

Impact of newborn screening on value assessment of arsa-cel:

The economic model will evaluate both pre-symptomatic and early symptomatic patients treated with arsa-cel; and as previously mentioned the achievable health outcomes for ES-EJ patients are different to those patients treated pre-symptomatically. The importance of early diagnosis and initiation of treatment is now increasingly recognised for a number of rare genetic conditions and inborn errors of metabolism, with the most beneficial response to treatment observed in patients prior to the onset of symptoms.⁵

Specifically for MLD, this is because patients treated in the early symptomatic stage of the disease or who are close to the predicted age of onset will incur some irreversible cell damage as a result of the sulfatides that accumulate during the engraftment phase for arsa-cel before the levels of the ARSA enzyme are sufficient to break them down. The damage done in this period then persists throughout the patients' lifetime; such that the

quality of life enjoyed by these patients is not perceived by the general population to be as great as those patients who show no manifestations of the disease.

There are multiple global newborn screening pilots for MLD that have either completed or are currently under way, including one prospective pilot in the US. Published data from a retrospective anonymized newborn screening pilot in the US in over 27,000 newborn dried blood spots demonstrated near 100% assay specificity.⁶ Furthermore, results from a prospective newborn screening pilot in Germany in over 80,000 newborn dried blood spots identified three cases demonstrating proof of concept of the feasibility of a high-throughput method for MLD newborn screening.⁷ Thus, there is ultimately the potential to treat all patients pre-symptomatically and well before the predicted onset of symptoms.

Consequently, it is important that the economic analysis captures the full potential value of arsa-cel; and as such a scenario should be included where all treated patients are modelled to achieve health gains comparable to the healthy general population. Whilst Orchard Therapeutics recognises this will probably be the most optimistic scenario, it is also likely to be the most reflective of the real world once newborn screening is routinely established.

Modified societal perspective analysis:

Orchard Therapeutics welcomes the fact that if the data allows, ICER will include a modified societal perspective that incorporates future productivity gains and other indirect costs such as lost family income and out of pocket costs, and will also consider this perspective as a co-base case when the societal costs of care are large relative to direct health care costs. Given that all untreated early-onset MLD patients have either died or are in a vegetative state by employment age, coupled with the high caregiver burden (caregivers spend an average of 15 hours per day caring for an affected child), the societal perspective will be an important consideration in determining the value of arsa-cel.

In a study in the Netherlands, Bean *et al*⁸ showed that there are significant potential productivity gains for patients treated with arsa-cel compared to untreated patients who do not have opportunities to enter the workforce; and significant family income is lost through non-treatment particularly in the later stages of MLD. The authors showed that in untreated patients over a 30-year timeframe, the estimated family income lost as a result of caring for a MLD patient was €214,416 using a 3.5% discount rate for time preference. Conversely, in an arsa-cel treated patient, the potential productivity gains accrued over a working life were estimated at €317,484 (3.5% discount rate) compared to €0 for untreated early onset MLD patients.⁸

It is likely that a similar or greater impact on future productivity gains and lost family income would be realized if a similar estimation were conducted in the US.

Budgetary Impact Analysis:

An important consideration for the budgetary impact analysis (BIA) referred to in the scope is the potential population eligible for treatment. More specifically, a number of adjustments will be required, as it is not just the direct application of the MLD incidence/birth prevalence of MLD number for determining the number of patients in the BIA. For example, late infantile MLD is the most common MLD phenotype accounting for 50-60% of all MLD cases; however in the absence of newborn screening the only way to identify an LI patient pre-symptomatically is if they have an older affected sibling who will not be eligible for treatment and who will unfortunately die of the disease. In this case all siblings of the index case (proband) would undergo genetic testing to ascertain whether they have MLD or not.

Clinical experts in the management of MLD estimate that approximately 32% of all LI cases are identified due to family history of the disease, meaning that 68% of all LI patients would not be eligible for treatment. To illustrate this, if 36 babies are born with MLD per year in the US of these 20 would have the late infantile phenotype, and of these only 6 would have a family history of MLD and therefore be identified pre-symptomatically and thus be eligible for treatment. A similar premise applies to pre-symptomatic EJ patients.

For ES-EJ patients, the window for treatment from onset of symptoms to becoming ineligible is very narrow. In a study by Fumagalli *et al*, the median time from onset of symptoms to >GMFC-MLD 1 (and therefore ineligible for treatment) for early juvenile patients was just under 7 months.¹ Given the rarity of the disease, there is often a delay in diagnosis which means that a large proportion of ES-EJ patients are not diagnosed in time. Again, clinical experts in the management of MLD estimate that less than 20% of EJ patients who have some symptoms of disease will be diagnosed within the treatment window for arsa-cel.

References

- ¹ Fumagalli F, Zambon AA, Rancoita PMV, et al. Metachromatic leukodystrophy: A single-center longitudinal study of 45 patients. *J Inherit Metab Dis* 2021.
- ² Lum S, Srepian K, Gosh A, et al. Long-term survival and cardiopulmonary outcome in children with Hurler syndrome after HSCT. *Journal of Inherited Metabolic Disease* 2017;40:455-460.
- ³ Pang F, Campbell L, Howie K, Wilds A, et al. Quality of life of patients and their caregivers with MLD in US, UK, Germany and France. Poster presented at Annual WORLDSymposium, Feb 8-12, 2021.
- ⁴ Ara R, Brazier JE. Populating an economic model with health state utility values: moving toward better practice. *Value in health: the journal of the International Society for Pharmacoeconomics and Outcomes Research* 2010;13(5):509-18.)
- ⁵ Bessey A, Chilcott J, Pandor A, Paisaley S. The cost-effectiveness of expanding the UK Newborn Bloodspot Screening Programme to include five additional inborn errors of metabolism. *International Journal of Neonatal Screening* 2020;6, 93.
- ⁶ Hong et al. 2020. Toward newborn screening of metachromatic leukodystrophy: results from analysis of over 27,000 newborn dried blood spots. *Genetics in Medicine*. doi.org/10.1038/s41436-020-01017-5.
- ⁷ Oliva P, Mechtler T, Schwarz M, et al. Newborn Screening for MLD in Northern Germany -a prospective study. Poster presented at Annual WORLDSymposium, 22-26 Feb 2023.
- ⁸ Bean K, Olaye A, Velikanova R et al. The societal costs of MLD in the Netherlands. *Value in Health* Vol 25(7): Supplement S344. July 2022. Doi.org/10.1016/j.val.2022.04.299.