Attn: The Institute for Clinical and Economic Review (ICER)

Subject: Response to ICER's Report on Gene Therapy for Metachromatic Leukodystrophy

To whom it may concern:

As leukodystrophy experts, we are writing in response to ICER's recent report on gene therapy for Metachromatic Leukodystrophy (MLD), which has significant implications for this progressive and devastating condition.

While rare, MLD is one of the most common leukodystrophies (1, 2). Encompassing over half of the cases, the late infantile form of MLD, which has its onset before 2.5 years of age, is characterized by a rapid motor and cognitive regression and results in death years later (3). The juvenile MLD (J-MLD) subtype is often divided into two categories: early and late juvenile. The duration and severity of the clinical course is thought to bridge the rapid decline found in the late infantile variant and the slower progression of the adult form, although once independent ambulation is lost, the rate of decline is rapid (4). The distinction between progression between early juvenile and late juvenile forms can be minor, with a difference in progression of months. After a rapid period of neurologic loss, affected children continue to live for years after having lost the ability to move. Cognitive skills are lost typically *after* motor skills are lost. Of importance, there is not a 'mild' form of MLD. This is a universally progressive and devastating disorder.

Even among the leukodystrophies, metachromatic leukodystrophy is notable for its severe and rapid neurologic decline (5-7). Overall, children with leukodystrophies have a low health-related quality of life (8-11), and hospitalizations cost over \$59 million per year (9). Currently in the US, there is an unmet need for targeted therapies, and medical care is limited to palliation and support. Our affected patients require *many years* of intensive care beginning within months of diagnosis. The relentless loss of cognitive and

motor functions, worsening tolerance for food/feedings, the diminishing quality of life, and the emotional toll on both patients and their caregivers underpin the daily struggle endured by our families. This report underscores the critical importance of evaluating novel treatments for rare diseases like MLD, where the impact on patients and their families is immeasurable. We would like to emphasize the profound burden that MLD places upon affected individuals and the urgent, unmet need for effective therapeutic options.

Before gene therapy became a possibility, there was limited hope in the community. This report underscores the transformative and enduring impact of gene therapy, especially when offered to presymptomatic children. Within the near future, we can envision a world in which children are diagnosed by newborn screen and treated *before* myelin and nerve injury occurs, dramatically changing the disease course with a single intervention.

As this report continues to shape discussions around MLD gene therapy, we urge ICER to recognize the gravity of the disease and the transformative impact that equitable access to gene therapy could have on our future patients' lives. Thank you for your commitment to advancing patient-centered analysis that guides the way towards better treatments and improved quality of life.

Sincerely,

Adeline Vanderver, MD Program Director of the Leukodystrophy Center of Excellence Jacob A. Kamens Endowed Chair in Neurological Disorders

Laura Adang, MD PhD MSTR Assistant Professor of Neurology Program Direction Predoctoral Preparatory Program

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**Amy Waldman, MD MSCE** Associate Director, Neurology Gene Therapy Medical Director of the Leukodystrophy Center of Excellence

# **The Children's Hospital** of Philadelphia<sup>®</sup>

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- 1. Kehrer C, Elgün S, Raabe C, et al. Association of age at onset and first symptoms with disease progression in patients with metachromatic leukodystrophy. *Neurology*. 2020.
- 2. Biffi A, Cesani M, Fumagalli F, et al. Metachromatic leukodystrophy mutation analysis provides further evidence of genotype-phenotype correlation. *Clin Genet.* 2008;74(4):349-357.
- 3. Kehrer C, Elgün S, Raabe C, et al. Association of Age at Onset and First Symptoms With Disease Progression in Patients With Metachromatic Leukodystrophy. *Neurology*. 2021;96(2):e255-e266.
- 4. Biffi A, Montini E, Lorioli L, et al. Lentiviral hematopoietic stem cell gene therapy benefits metachromatic leukodystrophy. *Science*. 2013;341(6148):1233158.
- 5. Dali C, Sevin C, Krägeloh-Mann I, et al. Safety of intrathecal delivery of recombinant human arylsulfatase A in children with metachromatic leukodystrophy: Results from a phase 1/2 clinical trial. *Mol Genet Metab.* 2020.
- 6. Sessa M, Lorioli L, Fumagalli F, et al. Lentiviral haemopoietic stem-cell gene therapy in earlyonset metachromatic leukodystrophy: an ad-hoc analysis of a non-randomised, open-label, phase 1/2 trial. *Lancet*. 2016;388(10043):476-487.
- 7. Beschle J, Döring M, Kehrer C, et al. Early clinical course after hematopoietic stem cell transplantation in children with juvenile metachromatic leukodystrophy. *Mol Cell Pediatr*. 2020;7(1):12.
- 8. Saute JA, Souza CF, Poswar FO, et al. Neurological outcomes after hematopoietic stem cell transplantation for cerebral X-linked adrenoleukodystrophy, late onset metachromatic leukodystrophy and Hurler syndrome. *Arg Neuropsiquiatr.* 2016;74(12):953-966.
- 9. Groeschel S, Kühl JS, Bley AE, et al. Long-term Outcome of Allogeneic Hematopoietic Stem Cell Transplantation in Patients With Juvenile Metachromatic Leukodystrophy Compared With Nontransplanted Control Patients. *JAMA Neurol.* 2016;73(9):1133-1140.
- van Rappard DF, Boelens JJ, van Egmond ME, et al. Efficacy of hematopoietic cell transplantation in metachromatic leukodystrophy: the Dutch experience. *Blood*. 2016;127(24):3098-3101.
- 11. Solders M, Martin DA, Andersson C, et al. Hematopoietic SCT: a useful treatment for late metachromatic leukodystrophy. *Bone Marrow Transplant*. 2014;49(8):1046-1051.
- 12. Martin HR, Poe MD, Provenzale JM, Kurtzberg J, Mendizabal A, Escolar ML. Neurodevelopmental outcomes of umbilical cord blood transplantation in metachromatic leukodystrophy. *Biol Blood Marrow Transplant*. 2013;19(4):616-624.

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- 13. Mirchi A, Pelletier F, Tran LT, et al. Health-Related Quality of Life for Patients With Genetically Determined Leukoencephalopathy. *Pediatr Neurol.* 2018;84:21-26.
- 14. Brimley CJ, Lopez J, van Haren K, et al. National variation in costs and mortality for leukodystrophy patients in US children's hospitals. *Pediatric neurology*. 2013;49(3):156-162.e151.
- 15. Nelson C, Mundorff MB, Korgenski EK, Brimley CJ, Srivastava R, Bonkowsky JL. Determinants of health care use in a population-based leukodystrophy cohort. *J Pediatr*. 2013;162(3):624-628.e621.
- 16. Bonkowsky JL, Nelson C, Kingston JL, Filloux FM, Mundorff MB, Srivastava R. The burden of inherited leukodystrophies in children. *Neurology*. 2010;75(8):718-725.

Dear ICER Review Committee:

The report for MLD-gene therapy (Arsa-cel) with details several key findings and gives a detailed insight into the potential benefits and costs of this therapy. As the long term data for Arsa-cel continues to show stable neurocognition, it would be prudent to not limit the cognitive benefits to 10 years currently. As we continue to follow these children, especially those with the late-infantile and early juvenile cohorts, there is stable enzyme level of ARSA in these children. The comparative cohort in most of these instances is often deceased by 10 years of age. The survival as well neurocognitive and motor benefit of this therapy continues to be superior to the natural history.

One of the challenges of this report is the extrapolation of data from limited sample size, especially in cost comparison for loss of wages and out of pocket costs for caregivers. Some of these challenges are highlighted on page 32 of the repot under the section "Uncertainties and Controversies". In rare diseases, as reported by Project Alive, the indirect costs are a significant metric which often goes unnoticed. Objective assessment of GFMC based criteria are used to assess costs and benefits, but many of the indirect measures including caregiver burden on the family need to be further considered. There are several areas highlighted by the authors of this report which discusses the potential for longer term benefit of Arsa-cel compared to the current standard of care. As more data will potentially further strengthen the model in the next few years, this report can further discuss the scenarios and also consider perspectives from the families with children or adults living with MLD.

Ashish Gupta MD, MPH Assistant Professor Pediatric Blood and Marrow Transplant University of Minnesota

### Dear ICER colleagues,

I write to respond to your report mentioned above. I am an academic paediatrician in Manchester, UK and I have been active in the field of stem cell transplantation and stem cell gene therapy for lysosomal disorders for over 15 years. I also run the largest clinic for children with lysosomal storage disorders in Europe. I was a clinical expert witness for the NICE appraisal of this product and worked with NICE, NHS England, NHS Scotland and Orchard therapeutics to reach a position in which this therapy could be used routinely. I also lead the only centre in the UK for the treatment of MLD with arsa-cel (Libmeldy) and our first year's experience in the clinic is summarised recently in Horgan et al 2023.

I write to comment specifically on the question of durability of response. I note in the report you produce you limit the benefit of arsa-cel to 10 years, presumably based on the fact that follow up from the Milan trials does not extend much beyond this time and that a small minority of patients have shown clinical decline following treatment.

I have clinical experience from 4 different ex vivo lentiviral vectors and following up over 100 allogeneic transplanted LSD children. Unlike in the AAV field (where I have also experience) there is no evidence thus far from long term clinical experience or on a biological basis to support a drop off in gene expression and therefore enzyme levels with this therapy approach. There is evidence for much longer than 10 years, especially in the primary immune deficiency world, showing continued expression for as long as follow up is continued. When I review the outcome data biologically there is excellent supraphysiological enzyme expression in all patients. The clinical data is more nuanced however which I understand can lead to concern. In my view the variability in the clinical data comes down in almost all cases to patient selection and this is a key reason why the license in Europe for Libmeldy is more restrictive than the original trial criteria. This is also why, in the UK, every case is discussed and assessed twice by a multi-disciplinary team to try and ensure the optimal patient selection and therefore outcome.

We have 35 year outcomes for both MPSI (Hurler) allogeneic transplants and in neuronopathic Gaucher disease (Lum et al 2017, Donald et al 2022). In all the long term cases enzyme expression by donor cells is stable, clinical outcomes change over time but in most cases related to inadequate enzyme secretion. We believe in ex vivo lentiviral stem cell gene therapy we have overcome the dosing question, we now need to focus on the age at diagnosis and newborn screening.

I would be more than happy to discuss these issues further if helpful,

Prof Simon Jones Consultant paediatric inherited metabolic disease Medical Director, NIHR Children's clinical research facility Manchester University NHS Foundation trust University of Manchester

### ICER Atidarsagene Autotemcel for Metachromatic Leukodystrophy

I am a pediatric neurologist specializing in leukodystrophies and have cared for many patients with both presymptomatic and symptomatic Late infantile and Early Juvenile forms of metachromatic leukodystrophy. I have had patients whom have been treated with stem cell transplant, gene therapy, or nothing. I feel the data has shown significant improvement from the natural history as well as those treated with transplant. There are certainly gaps in the knowledge regarding these treatments due to the lack of a control groups with this study. Also as it is a rare disease the sample sizes in all groups are small. The treated patients have been followed for a significant period of time, however all long term side effects may not be known at this time.

The report was a well put together analysis of the treatment and our gaps in knowledge. However, the numbers and reports fail to consider the real life impact of disease on the patient and their families. MLD is a horrible disease causing loss of skills, difficulty sleeping, seizures, spasticity, and systemic symptoms such as gallbladder disease, peripheral neuropathy, and GI symptoms. Although, this treatment may not completely cure MLD or prevent all future progress, the patients will have significant improvement from there natural disease course. The patients with early symptomatic disease may slow their progression and limit the severity of their disease with treatment. In the case of early juvenile MLD, their disease typically progresses more slowly but they may progress quickly for a few years and then stabilize with severe disabilities. Treatment with atidarsagene autotemcel will allow the patients to live a more enjoyable and productive life that without treatment. Transplant has not shown improvement/prevention of MLD Related peripheral neuropathy which this drug seems to help with prevention in MLD.

In rare life-threatening diseases, the nature of the disease often limits knowledge and study design. Due to the severity of metachromatic leukodystrophy, waiting for additional studies to be completed prior to approval would allow more children to die waiting on a therapy. Leniency must be granted regarding these rare devastating diseases where there are no current effective treatments. Delaying or preventing disability is expected to make huge improvements in the qualify of life of patients. Please allow these children with MLD the opportunity lead longer and fuller life.

Thank you, Stephanie Keller, MD To Whom It May Concern

I am responding to the economic analysis that assume the duration of benefit with Arsa-cel to be 10 years.

In my professional opinion as a Bone Marrow Transplant physician with expertise in children with inherited metabolic disorders including metachromatic leukodystrophy, I am concerned about this assumption, even though stated in the document as conservative. Arsa-cel are gene corrected autologous hematopoietic stem cells that give rise to enzyme producing cells and the expected duration of benefit would be lifelong. This is the assumption with allogeneic hematopoietic cell transplant for various genetic disorders as well. Given that the follow up data is through 11 years, it is reasonable to state that though limiting the duration of benefit to 10 years seems very conservative and probably inaccurate.

Thanks for your consideration,

Sincerely,

Sandhya Kharbanda, MD Professor of Clinical Pediatrics Medical Director and Section Chief, Pediatric Bone Marrow Transplant Benioff Children's Hospital, San Francisco University of California, San Francisco 1975, 4<sup>th</sup> Street, 6<sup>th</sup> Floor, C6908 San Francisco, CA 94158 Phone: 415-476-2188



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

August 22, 2023

Institute for Clinical and Economic Review 14 Beacon Street, Suite 800 Boston, MA 02108 via email: publiccomments@icer.org

Re: Draft Evidence Report of Atidarsagene Autotemcel for Metachromatic Leukodystrophy

Dear Reviewers,

MLD Foundation respectfully submits these comments as informed by our 24-year history of working directly with hundreds of families, dozens of biopharma/pharma/institutions, and a broad swath of international researchers.

### **Executive Summary & Rating Matrix (page 19)**

MLD Foundation was an external Expert Reviewer for ICER s Draft Evidence Report of Atidarsagene Autotemcel for Metachromatic Leukodystrophy. We were surprised to see the drop from a B+ to a C+++ for early symptomatic EJ MLD from the draft we reviewed to the current public draft.

During our initial draft review, we were not in total agreement with the B+ rating, but after reading ICER's rationale, we accepted the B+ rating since there is some uncertainty about the benefit of treatment in EJ children who are early symptomatic. However, the magnitude of benefit over the current treatment of bone marrow transplant is greater with GT. While not all children may return to a normal state of health, the majority of early symptomatic EJ children we know who have received arsa-cel are still far better off than those treated with traditional HSCT transplant or no treatment at all. For those with early symptomatic EJ, the risks are greater than pre-symptomatic, but outcomes of those treated still suggest the risk/benefit assessment is still in the B category.

In the public draft, the paper quoted, "treatment with busulfan carries a risk of death, long-term outcomes are less certain, and it appears possible that treatment initially hastens progression of physical and cognitive decline before stabilizing that decline." (*Ref 20*) This paper contains only 3 cases of early symptomatic EJ, and only one of those cases received busulfan in their conditioning. The paper doesn't break down the statistics of the three early juvenile cases but only speaks to the overall HSCT results. Using this extremely limited EJ HSCT data to assess autologous transplanted-based gene therapy is not a fair comparison. No research has been published to our knowledge that has examined whether GT negates the hastening effects of the physical and cognitive declines due to conditioning or due to GT having faster stabilization than the 12 to 24 months of HSCT. Perhaps this is why some of the early symptomatic EJ patients return to an almost normal state.

Table 3.3 shows ES-EJ-MLD as GMFM median of 48.36 with arsa-cel contrasted with 2.29 for natural history. That is a dramatic improvement.

Any treatment for MLD carries risks and unknowns. The partial benefits of GT are still better than the partial benefits of HSCT. We would like the rating for early symptomatic EJ returned to a B+. Ultimately, informed parents will weigh the potential risks/benefit of any treatment for their child based on the data available at the time and their own personal circumstances.

## **20 year Disease Stabilization** ... Page 16, ES2, Table 4.1 and 4.2

Table 4.1, row 1 and Table 4.2 ... We find it confusing that "full response" patients are defined as having a period of stabilization followed by a decline similar to natural history. It is not at all clear to us why the decline would be the same as natural history. We would expect either no decline or a significantly slower decline than natural history. The rate of decline assumption will dramatically affect the modeled results. Further, the "stable partial responders" are defined as some decline then stability. This is inconsistent with "full response " patients, where the therapy is assumed to lose its efficacy after some period of time. Why would the stability for partial responders be permanent when the therapy for full responders is not? And to further reinforce the concern that full responders do not decline at the rate of natural history, the "unstable partial responders" are described as having a slower than natural history progression. We request that these definitions and the derived models be carefully reconsidered.

Table 4.1, row 2 ... While there clearly is no observed proof of 50, 30, or even 20-year therapeutic stability, it is important to note that most patients retain full or significant mobility and that only a small handful of patients received therapy at the earliest stages of development where non-observable progression is minimized. We suspect, and perhaps a re-analysis of the data will show, that the further the progression, observable or not, i.e., age at the time of therapy, is the key factor influencing the rate of motor decline. The ideal time for therapy is as soon as practical after identification at birth. To date, with just a few patients falling into this category, therapy has been given at 6-9 months. MLD newborn screening is well-studied and will become universal over the next five years, so the trends will shift to earlier diagnosis and more effective outcomes.

Table 4.1, row 2 ... While the NICE and FINOSE models were adjusted from the manufacturer's 50-year stabilization to 20 and 15 years, respectively, we should not assume the purpose of those adjustments aligns with the purposes of the ICER analysis or that those adjustments reflect any change in actual expectations of outcome stability. Modeling with a shorter length of stability is more conservative in terms of outcome. However, it would be reasonable to additionally model at 30 or even 50 years to provide perspective.

### Harms ... page 15, page 19 2nd paragraph

Most of the harms are attributed to transplants, and the data shows these events are survivable without long-term harm. It is also not emphasized that area-cel is infused using an autologous transplant. This distinction is key when comparing area-cel transplant impacts to traditional HSCT impacts, especially in the peri-transplant period.

We strongly request that an additional harm be considered ... that being the lack of access to arsa-cel (when eligible). Those patients will die (See E3.1 - E3.3). These patients not only die, they progress through all of the phases of GMFM, and they miss out on the life and life goals they would live even if gene therapy was sub-optimal, which frankly, the data refutes. In addition to the patient's death, the family suffers the progression and loss. We should include lack of therapy as a harm and incorporate it into the value aspects of the model.

Summary & Comment, page 18: "as reflected in the improvement in both primary and secondary endpoints, extending survival, *and avoiding the reduced quality of life and much quicker death with no therapy*.".

Page D7 ... this section should also reflect that no therapy leads to quicker progression into all of the levels of GMFM, i.e., poor quality of life, and to a certainty of earlier death than the comparatively much lower risk of harm from therapy.

### Drug Costs ... page 26

It should be noted that many gene therapy companies, including Orchard Therapeutics, are lobbying for the ability to provide contractual guarantees with credits or rebates if the therapy does not work for a given patient (MVP Act). This sort of sales agreement moves risk to the drug company and puts them "in the boat" with the patient" as far as risk for a successful outcome goes. No other therapy class offers these sorts of risk management provisions. This needs to be reflected and incorporated into the ICER model.

# **Diagnosis and Clinical Course of MLD** ... A3

*re:* Trinidad et al. Genome Biology (2023) 24:172 Predicting disease severity in metachromatic leukodystrophy using protein activity and a patient phenotype matrix

Patient-based data were used to develop a phenotype matrix that predicts MLD phenotype given ARSA alleles in a patient s genotype with 76% accuracy. We then employed a high-throughput enzyme activity assay using mass spectrometry to explore the function of ARSA variants from the curated patient data set and the Genome Aggregation Database (gnomAD). We observed evidence that 36% of variants of unknown significance (VUS) in ARSA may be pathogenic. By classifying functional effects for 251 VUS from gnomAD, we reduced the incidence of genotypes of unknown significance (GUS) by over 98.5% in the overall population.

The above reference should be reviewed for inclusion and updating of the conclusion in the last two sentences of A3, paragraph 1. There is a good genotype-phenotype correlation for the great majority of variants seen in the general population. Additionally, MLD Foundation is validating the conclusions and academically/bench-derived geno-pheno correlation with real-world patient data.

Second paragraph .. "... children with LI-MLD ..." should read " ... children with LI/EJ-MLD ..." and "The juvenile form often presents ..." should read "The late-juvenile (LJ) form often presents ..."

## **Contextual Considerations and Potential Other Benefits**

• Table 5.2, block 1: "Substantial impact" is a severe understatement. As Figure E3.1 shows, PS-LI-MLD children are unable to experience any life goals by age 4 as they are at GMFM level 5.

# **Clarifying Comments**

- Executive Summary, paragraph 2, page ES1: "Initial symptoms of LI/EJ MLD..."
- PSAP gene Background page 1: It was correctly noted that PSAP/saposin B is an activator but it does not say that it activates ARSA that should be noted. It should also be noted that PSAP problems are not resolved by arsa-cel.
- Newborn Screening page 2, 2nd paragraph: might be clarified by "... since there is no *widely implemented* newborn screening ..."
- Autologous transplant page 2, 2rd paragraph: It would be informative to enhance "... cells are harvested from the patient (*arsa-cel is an autologous transplant*)."
- Uncertainty and Controversies page 16, 2nd paragraph: Are single-arm studies where the control is a sibling subject to the bias referred to in this paragraph? Many of the Clinical trial patients had older siblings as controls.
- Monthly Costs page 27: We cannot argue with these numbers as we do not have concrete evidence to refute them, however, with regard to the care of Lindy, our 42 year old LJ-MLD daughter, her monthly drug costs are in excess of \$3,000 and her medical visit costs (cost, not out of pocket) are probably closer to \$2,000 per month (6-7 visits/mo). As a small offset for these higher expenses, we try not to go to the hospital more than once a year.

We appreciate the extensive research and effort put into this Draft and the arsa-cel model. We look forward to the incorporation of some or all of the feedback above.

Teryn Sul

Sincerely,

Teryn Suhr, Executive Director

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Dean Suhr, President MLD Foundation

### Orchard Therapeutic's Response to the ICER Draft Evidence Report of Atidarsagene Autotemcel (arsa-cel) for Metachromatic Leukodystrophy (MLD)

Orchard Therapeutics appreciates the opportunity to comment on the draft evidence report for the Institute for Clinical and Economic (ICER) review of arsa-cel for the treatment of MLD. We would like to first thank ICER for delivering a comprehensive analysis and complex health economic model in such a short timeframe. With ICER's efforts and its willingness to engage various stakeholders during the review process are appreciated, we believe there are several important areas that should be revised in the evaluation. These are described below with recommended suggestions for updating the draft evidence report (DER) and health economic model:

# **Detailed Comments and Recommendations**

- 1. Respectfully, we disagree with ICER's C++ comparative effectiveness assessment applied to arsa-cel for the treatment of early symptomatic early juvenile MLD based on ICER's justification that arsa-cel treatment may hasten motor and cognitive decline compared to natural history. The DER infers that the reason for the C++ rating is that treatment could initially hasten progression of physical and cognitive decline before stabilizing and treated patients would have to deal with the consequences of bone marrow conditioning with only partial benefit. However, this is inconsistent with what has been observed in the clinical trial data.
  - The inference of accelerated disease progression was based upon conclusions from the Beschle study<sup>1</sup> in allogeneic HSCT which is not applicable to arsa-cel.
  - Further this inference was based upon observations of the time from treatment to death of two symptomatic EJ patients whose baseline disease characteristics are outside of the scope of this appraisal. As a reminder, the families of the two treated symptomatic EJ patients both rejected insertion of a G-tube once the patients experienced dysphagia, after progressing to GMFC-MLD 5 and 6. Whilst, at first glance, these patients would seem to have progressed more rapidly in the later GMFC-MLD stages, the "time to death" metric used to illustrate this progression did not account for carer attitudes and decisions. The rapidly progressive phase of MLD is from GMFC-MLD 2 to 5. After GMFC-MLD 5, the duration of time spent in these stages is largely based on the degree of palliative care the carers are prepared to undertake to prolong life. The time taken to transition from GMFC-MLD 2 to 5 in the two treated symptomatic EJ patients that died was comparable to the time taken to transition from GMFC-MLD 2 to 5 in the natural history data, rather than a more rapid progression.
  - Regarding the cognitive decline of arsa-cel treated ES-EJ patients, the clinical data do not suggest that arsa-cel treatment hastens cognitive decline in ES-EJ before stabilizing that decline. One substantial benefit of arsa-cel treatment compared to standard of care is the preservation of cognitive function even if patients have incurred some motor dysfunction prior to arsa-cel treatment. Although some of the arsa-cel treated ES-EJ patients progressed to GMFC-MLD 3 or 4, these patients have retained normal cognitive function. Comparatively, in the natural history (NHx) cohort, the majority of patients at the same GMFC-MLD level had severe cognitive impairment. In fact, ICER also stated in the DER: "Of note, cognitive function did not decline in the majority of patients with EJ-MLD treated with arsacel even with some motor impairment (i.e., higher GMFC-MLD level) whereas it severely declined for those in the natural history cohort even at early stages of motor impairment." (Page D12). The implications of normal cognitive function in arsa-cel treated patients are the retention of independence, attendance at school/university and interaction with their peers and these individuals are all associated with a better quality of life than those who are severely mentally incapacitated. It is, therefore, surprising that the summary of benefit for the ES-EJ cohort doesn't recognize this aspect and instead infers that cognitive decline is hastened. Finally, a recent publication by Martin et al. evaluated meaningful changes in physical functioning and cognitive declines in MLD through caregiver interview. The authors reported that caregivers felt that GMFC-MLD and ELFC-MLD accurately described motor and language declines in their children, respectively. Most caregivers (10/12) reported that the idea of delaying disease progression would be meaningful. Further, a slowing of motor function decline in GMFC-MLD, from category 1 to category 3 or from category 2 to category 4 over 2 years, was seen as meaningful by all caregivers asked. Caregivers also reported that delaying expressive language decline at any level that did not indicate a complete loss of expressive language (indicated by categories 1-3) would be meaningful<sup>2</sup>.

In summary, given the above evidence, we respectfully ask ICER to:

- Remove the text suggesting that treatment with arsa-cel may lead to a rapid disease progression.
- Re-assess the comparative effectiveness of arsa-cel in the ES-EJ population.
- 2. We find that ICER's assumption of a 20-year durability of effect for <u>all</u> full and stable partial responders treated with arsa-cel is overly conservative and a gross underestimation of treatment benefit due to the mechanism of action, already 12 years of clinical data, underlying biomarkers, and precedents set in other disease areas would justify a proportion of patients to receive a lifetime durability of effect.
  - A significant reason for the expectation of prolonged durability of effect (i.e., greater than 20 years) is related to the mechanism of action of arsa-cel, Essentially, gene-corrected CD34+ HSPCs contain one or more copies of the human ARSA cDNA sequence and after myeloablative conditioning, these infused gene-corrected cells engraft and repopulate the hematopoietic compartment. The myeloid progeny of these cells migrates across the blood brain barrier to reconstitute resident microglia in the brain and differentiate into endoneurial macrophages in the PNS. Gene corrected cells synthesize the functional ARSA enzyme at normal to supranormal levels and ARSA secreted into the extracellular matrix and taken up by surrounding cells leads to the breakdown of harmful sulfatides. This prevents or slows brain and PNS demyelination, neurodegeneration, and atrophy, processes that underlie the clinical manifestations of MLD. In addition, replacing ARSA-deficient microglia with gene-corrected, ARSA-expressing microglia addresses the inflammatory and apoptotic aspects of MLD mediated by abnormal microglial activation and restores normal microglial function, including scavenging of excess extracellular sulfatides. Consequently, after successful and stable engraftment of gene-corrected HSCs the effects of arsa-cel are expected to be persistent, as progeny will continue to be generated indefinitely and all progeny have the corrected gene for ARSA enzyme production.
  - Reconstitution of ARSA activity in PBMCs to normal or supranormal levels and ARSA activity in CSF to normal levels was sustained throughout the length of follow-up, which was over 12 years in the earliest treated subject (PS-LI) and showed no trend to diminishing (Figure 1). Data from Scala et al.<sup>3</sup> looking at the dynamics of genetically engineered hematopoietic stem and progenitor cells after autologous transplantation in humans showed similar results. Therefore, a stabilization period of 20 years, with an assumption that thereafter all patients progress, lacks biological plausibility. In other words, there is no biological reason to support the assumption that after 20 years, progeny cells carrying the corrected gene would suddenly stop producing the ARSA enzyme.
  - We maintain that ICER's assumption of the 20-year durability of effect based on previous assessments of arsa-cel by NICE and FINOSE does not reflect the latest clinical data cut provided to ICER. Furthermore, it is important to appreciate that the context of these discussions was not fully captured in their assessment reports. At the time of the earliest assessment by NICE which commenced in 2020, NICE selected 20 years as their base case for the following reasons:
    - Although recognizing the likelihood of durability of effect for over 20 years was high, there was still perceived uncertainty, given the lack of experience with HSC-based gene therapies with over 20 years of follow-up.
    - At the time of the NICE and FINOSE assessments, the clinical trial results available to these HTA bodies, were based on an average of only 2-3 years of follow-up with some of the later treated patients (classified as full responders) having less than 2 years of follow-up (note, although during the course of the HTA evaluation longer term data with follow-up of 5 years, were provided to NICE and FINOSE, this was for a limited group of patients and did not include data from patients in the expanded access programs (n=9 patients) some of whom had only 1-2 years of follow-up data).
    - $\circ$  At the time of the assessment, the additional n=10 patients treated with the cryo-preserved formulation had no clinical outcome data available.
  - However, since these assessments, each of the points highlighted above can be addressed with a greater level of certainty to support long-term durability due to augmentation of the evidence base.
    - The data from another autologous HSC gene therapy (Strimvelis) shows durability of effect beyond 20 years nearly 25 years showing continued durability of effect.

- Specifically, for arsa-cel, there are follow-up data for up to 12+ years (with an average of 8 years an additional 3 years' worth of follow-up since the NICE and FINOSE HTAs) demonstrating preserved durability of effect for full responders. This length of follow-up is in excess of many gene therapies that have been approved in the US, of which some have been previously reviewed by ICER.
- There are clinical outcomes for up to 4 years (average of 2.5 years) available for patients treated with the cryo-preserved formulation affirming the sustainability of the treatment effect.
- In addition, with specific reference to the comment in Table 4.1 of the DER, "However, updated data analyses submitted to other HTA agencies such as FINOSE and NICE report a decline in motor function after 2-3 years of stability," we would like to clarify that during the initial stages of these HTA appraisals, patients' response status was originally classified based on GMFC-MLD alone. Following feedback from NICE during the review process, we classified patient response using a more holistic and robust method through observing a multitude of outcomes (GMFM, MRI, DQp, PBMC ARSA and NCV) alongside GMFC-MLD to better determine stabilization. This is evidenced by comparing the previous proportions of unstable partial responders from the FINOSE assessment (which was used prior to this reclassification) with the WORLD 2023<sup>4</sup> data, which we provided for use in the ICER health economic model.
- The mechanism of action of arsa-cel is broadly based on the principle of allogenic haematopoietic stem cell transplants (HSCT), which have shown ongoing durability of effect for metabolic patients beyond 30 years. Arsa-cel leverages the same HSCT platform to be able to self-propagate and renew and involves the direct integration of the corrected gene into the genome unlike *in vivo* gene therapies. This is supported by experienced clinical experts in HSCT transplantation for lysosomal storage diseases. Professor Rob Wynn indicated that the demonstration of stable vector copy number (VCN) and polyclonality in autologous HSC gene therapy is analogous of stable donor cell engraftment and chimerism in allogeneic transplantation<sup>5</sup>. In the allogeneic setting, stable initial engraftment is predictive of stable long-term engraftment, which then translates to stable biochemical correction, clinical outcomes, and survival. The observation of stable VCN and polyclonality for arsa-cel in his opinion indicates that the autologous cells will continue to remain engrafted and correlate with long term clinical and disease response. Conversely, if a patient is going to fail with transplant, he/she will fail early, which gives confidence in the data showing consistent response rates over a longer period of time.
- HSCT has been used for over 50 years to treat patients with several diseases such as cancers, thalassaemia and sickle cell disease and has shown to be effective and life-long in preventing disease progression in these patients<sup>6</sup>. It is important to note that conventional allogeneic stem cell therapies carry the risk of graft failure due to immunological rejection of the transplant. Orchard would like to point out that the main reason why HSCT grafts fail is due to the body's immunological rejection of a recognised foreign body, which would not be the case with an autologous treatment such as arsa-cel. Hence whilst HSCT convenes long-term durability in several diseases, engraftment results with arsa-cel would be expected to be superior to allogeneic HSCT.
  - In the January 2023 periodic benefit: risk evaluation report (PBRER) for Strimvelis, for the treatment of ADA-SCID, Strimvelis was found to have 100% long-term survival for subjects in the study based on 2 to 23 years of follow-up data. The majority of subjects demonstrated evidence of engrafted gene-modified cells with sustained and maintained treatment benefits suggesting a lifetime durability of effect.
  - In the case of Hurler's Syndrome (MPS1-H), where patients receive similar HSC transplants as children, Prof. Robert Wynn confirmed that treated patients are above the age of 20 with maintained clinical response and cognitive function and no observation of waning of effect. In fact, for some of the earliest metabolic patients who were transplanted, they are now associated with follow-up of more than 30 years demonstrating long-term stabilisation. This observation is supported by data from Gardin et al. who followed MPS-1H patients treated with HSCT for up to 16.5 years and found that there were no signs of neurocognitive regression during follow-up (Figure 2)<sup>7</sup>.
  - Lastly, HSCT data from two long-term follow-up studies<sup>7,8</sup>, both show that if graft failure is to occur, it occurs soon after treatment administration. For the remainder of patients who do not

experience graft failure, there is expected to be long term stabilization, which again supports the longer-term time horizon for arsa-cel.

- The above evidence supports the potential for a lifetime durability of effect. Which we believe that a lifetime durability of effect should be assumed for all full and stable partial responders, we do recognise uncertainty in this parameter. Therefore, we propose that ICER in their base-case apply a lifetime durability of effect to the proportion of responder patients with at least 5 years of follow-up data (as evidence of sustained durability of effect) and the remaining full and stable and partial responders with the current 20-year durability of effect. A similar follow-up period of 5 years is also generally accepted and used in mixture-cure models for some cancer types, whereby a proportion of patients are considered "cured" (i.e., receive sustained lifetime durability of treatment effect) and are expected to have a survival benefit equal to the general population. This alternative is a similar methodology to what was used in ICER's assessment of beti-cel for beta-thalassemia.
  - This approach could be conducted using the clinical data reported in Table 1 documenting the percentage of patients classified as full or stable partial responders that have: (i) > 5 years of follow-up data; (ii) >8 years of follow-up data and (iii) >10 years of follow-up data.
  - To implement this proposal in the current ICER model, ICER could run their model first using the 20-year duration of stabilization and next using a lifetime duration of stabilization and then calculated a weighted average of these results based upon the proportions referenced in Table 1.
    - e.g., If lifetime durability is assumed for all full or stable partial responders that have > 5 years of follow-up, then the overall ICER would be weighted 59% lifetime to 41% having a 20-year stabilization period.
- In summary, given the above evidence, we respectfully ask ICER to:
  - Reassess the durability of a lifetime horizon and at a minimum consider the implementation for a proportion of patients.
  - Report the results of the 10-year and 50-year durability of effect scenarios in the main body of the evidence report and by MLD subtype (i.e., PS-LI, PS-EJ and ES-EJ) in addition to the currently reported aggregated result because of the large impact the durability of effect has on the cost-effectiveness results.
- 3. When reviewing ICER's we identified that natural history transition probabilities were used for the 12month pre-stabilization period for stable partial responders. This led to a misalignment of the model GMFC-MLD stabilization stages and the clinical trial data (Table 2). To aid with correcting this issue while accommodating ICER's model design, we have calculated the following transition probabilities that would be more closely aligned with the clinical trial results (see the stable partial responder transition probabilities in Tables 3 and 4). These pre-stabilization transition probabilities can be readily inserted into the existing ICER model for stable partial responders in the first 12 months. The transition probabilities were calculated (or "calibrated") through an iterative process using the ICER model by triangulating the modelled number of stable partial responders at 12 months post-treatment (i.e., the start of the stabilization period) across the GMFC-MLD stages with the clinical trial results for stable partial responders. We do recognize this approach does not perfectly align with the clinical trial data, but as seen in Tables 3 and 4, these adjustments result in a very close and clinically plausible approximation of the expected number of patients stabilizing across GMFC-MLD stages when using the ICER model design.
  - We respectfully request that ICER update their implementation of the pre-stabilization period for stable partial responders to align with the clinical trial data.
- 4. In the ICER health economic model base case, ICER used an adjusted (i.e., "recalibrated") version of the utility set provided by Orchard that did not allow for negative utility values. We appreciate that there is continued debate on the use of negative utilities, however, not allowing for negative health states requires deviation from the reported preferences of the US general population in valuing certain health states.
  - The concept of negative utility scores (i.e., health states worse than death) is supported by published literature, as studies in the US among healthy outpatients and those with serious illnesses show that a significant minority, and sometimes a majority, rate health states with severe cognitive impairment, such as severe dementia, as worse than death<sup>9,10,11</sup>. For example, quotes from carer's the PFDD for

MLD submitted to the FDA provide a vivid picture of what it is like living with an untreated patient with  $MLD^{12}$ 

- Our value set retains face validity when compared to other utility value set for similar severe progressive neuromuscular diseases and is comparable across all GMFC-MLD health states<sup>13</sup> (Table 5). This is corroborated further by a recent study by Lo et al<sup>14</sup>. estimating utility values for health states in MLD with TTO and EQ-5D utility values for GMFC-MLD 6 of -0.356 and -0.418, respectively.
- In addition, ICER's recalibration method to adjust negative utility scores introduces a floor effect, such that there is very little difference (i.e. 0.01) in the HRQL of a patient in GMFC-MLD 4 with moderate cognitive function who still has some motor function (i.e. able to sit or crawl and roll, and has head control), and is able to maintain awareness, communicate, recognize loved ones; as compared to a patient in GMFC-MLD 6 (bedridden, with no motor function) and has severe cognitive impairment and who is unable to do the aforementioned activities. Indeed, health states described as worse than death by patients in the US with one or more chronic illnesses included lack of awareness or inability to think, inability to communicate, inability to recognize loved ones, inability to make own decisions and progressive cognitive decline, particularly Alzheimer dementia<sup>15</sup>. Therefore, to have so little difference (0.01) in the HRQL of patients between these two health states makes the recalibration approach overall unreliable and lacking face validity.
- ICER's rationale for not permitting negative utilities was because it considered that "there are face validity concerns that as early as GMFC 3, where patients are still sitting without support, crawling, and rolling, participants rated this health state below 0." We would like to point out that patients in GMFC-MLD 3 with normal cognitive function and moderate cognitive function both have positive utility values of 0.38 and 0.10, respectively. It is the loss of cognitive function that leads to negative utilities, the impact of which has been validated in the literature mentioned above. Furthermore, whilst patients in GMFC-MLD 3 can crawl or roll, they cannot walk and require a wheelchair which was described in the vignette for GMFC-MLD 3. It is common knowledge that the loss of ambulation is perceived by the general public to have a significant impact on HRQL. Indeed, in the NICE appraisal of Elosulfase alfa for treating mucopolysaccharidosis type IVa, the accepted utility value for patients with normal cognitive function but who were wheelchair dependent was 0.08, which is lower than the 0.38 and 0.10 reported for GMFC-MLD 3 patients who are wheel-chair dependent with normal cognitive function or moderate cognitive impairment.<sup>16</sup> In addition, Hendriksz et al.<sup>17</sup> showed that children with MPS IVa who were confined to wheelchair reported utility values of -0.180, further supporting the plausibility of MLD patients in GMFC-MLD 3 and 4 having negative utility values.
- We respectfully request that ICER use our "unadjusted" utility value set, including negative utility values, in the base case of the model or as a scenario in the main body of the report. Whilst we appreciate that ICER had included these utility values in a sensitivity analysis in the supplemental information, Orchard considers that the utility value set it provided is a more accurate reflection of the HRQL in MLD.
- 5. In the ICER model base case, the same caregiver disutility (-0.068), for one carer, was applied to patients in GMFC-MLD 2 through to GMFC-MLD 6; such that carers of patients with MLD who are still able to walk with support and have no cognitive impairment have the same disutility as those caregivers of children who are completely immobile and in a vegetative state. This conflicts with the description of the caregiver burden in the DER, which describes an increasing caregiving requirement as MLD patient's progress. Section 2 of the DER states that, "*As MLD progresses and children lose motor and cognitive skills, the caregiving impact increases.*." It also states that often one or both parents need to leave work to care for their affected children. And therefore, this omission underestimates the total caregiver burden further by only applying the disutility to one caregiver.
  - Caregiver disutility scaling is further supported by the Lo et al.<sup>14</sup> who reported that TTO-based and EQ-5D-5L-based caregiver state utility values decreased from 0.928 and 0.864 (caring for patients at GMFC-MLD 1) to 0.454 and 0.246 (caring for patients at GMFC-MLD 6), respectively.
  - We respectfully request that ICER use the GMFC-MLD-scaled caregiver disutility set as the base case to be more accurately reflect the caregiver disutility based on disease severity by GMFC-MLD stage.

# Appendix 1

To place the value of arsa-cel into context, the experiences of clinicians, patients, carers and patient organisation have been provided below to offer a real-world perspective of the impact of both MLD as a disease and arsa-cel as a treatment. The data are taken from the PFDD for MLD meeting for the FDA that was held on 21 October 2022<sup>12</sup> and the ArchAngel MLD Trust response to the Evaluation Consultation Document committee papers issued as part of the NICE HST appraisal of arsa-cel in the UK, where the patient organisation ArchAngel MLD Trust canvassed opinions from clinicians globally and families of MLD patients.<sup>18</sup>

Orchard considers that all the testimonials provided help gauge the HRQL of patients and carers; add genuine, tangible real-world experience of arsa-cel that augment the measured clinical outcomes in the trials; and add some colour to clinical outcomes such as GMFC-MLD that might be difficult to visualise.

With regards to the impact of untreated MLD, the following testimonials were published:

Stacy, mother of five-year-old Brooks, living with late infantile MLD<sup>12</sup>:

"We would risk death. This is a horrific, terminal disease. We would be willing to try anything in order to get some quality of life back. We have nothing to lose at this point. Death is inevitable with this disease." Corrine, speaking on behalf of her son Trent, who passed away at the age of 29 from late juvenile MLD.

Susan, mother of Daniel, who passed away at the age of seven years from late infantile MLD<sup>12</sup>:

"The amount of equipment necessary that you have to move with you if you want to go anywhere. It's essentially a mobile PICU."

"It was mostly just trying to make him comfortable and for a long period of time, that was really difficult and almost impossible. ... The tone, muscle cramps, rigidity, and pain, and irritability were among the most difficult because we really had almost no way to control those symptoms. They were somewhat managed with clonidine and diazepam and other things, but really, our doctors seemed to be at a loss, and we were too."

"My parents had to add a bedroom to our house since we had no bedrooms on the main level. Ramps were also added to get into the house. We had a stander, a hospital-type lift bed, a rolling shower chair, and portable lift systems added so my parents could care for me. I had foam booties and a foam mattress pad to keep away bed sores, which we had problems with on my heels."

*"Children with this disease fall off a cliff within 90 days of symptom onset...children with the aggressive Late Infantile form lose everything in 90 days."* <sup>18</sup>

"Early onset MLD results in the loss of the ability to walk, sit and talk within months of onset."<sup>18</sup>

Whereas for patients treated with arsa-cel, the following testimonials were published by clinicians from across the globe: <sup>18</sup>

"I do not use this word lightly. It is a medical miracle. It is one of the greatest medical breakthroughs of our generation."

"Those having had gene therapy are doing extraordinarily well. Further, gene therapy patients identified because of an older sibling are universally surviving and thriving past the age of the death of their sibling."

*"We completely concur that gene therapy for MLD (as per the recommended patient populations) is truly transformative".* 

"With gene therapy we have the unprecedented opportunity to save the lives of children affected by MLD".

"The patients are truly remarkable and well outside anything that can be achieved with standard transplant."

"This is a dramatically effective therapy that will be life-changing and lifesaving for patients with MLD."

"Children who have been treated with gene therapy, I have witnessed them throw footballs and sing and dance and hug their parents and play video games and eat macaroni and pizza and hot dogs and lead remarkably normal lives".

The following is the perspective provided by patients and carers following treatment with arsa-cel:

Amy mother of Giovanni (treated with gene therapy in 2011):<sup>12</sup>

"My husband Brad and I had never heard of metachromatic leukodystrophy before our daughter, Livianna and son Giovanni were diagnosed in December 2010. Giovanni was just 11 months old and his three-yearold sister's symptomatic diagnosis led to him being tested and diagnosed. Just three weeks later, we were in Milan, Italy where Giovanni was the second child in the world to undergo gene therapy for MLD in February 2011.... After returning home from Milan in June 2011, Giovanni was a normal one- year-old outside of his hair growing back and his implanted port. We never had a single physical or medical complication or difficulty during or following his gene therapy. He has never had motor skill deficits or delays. At 12-years-old, Giovanni has never shown any symptoms of MLD."

Giovanni aged 12 (treated with gene therapy aged 1): <sup>12</sup>

"It is strange to hear when my mom talks about MLD because I just feel like a normal 12-year-old kid. I was a baby when I went through gene therapy... Gene therapy changed my life because well, I am here. Without gene therapy, my parents would only have photos and memories of me just like my sister, and that makes me sad to think about."

Les father of Cathal, who passed away at the age of six years from late infantile MLD and Ciarán treated with gene therapy aged 1 in 2017: <sup>12</sup>

"Ciarán, luckily, was eligible for the trial and he received that at age one... he was a little slow to start walking, but the treatment got a hold, and it arrested the progress of the disease in Ciarán's body, and he has been fine ever since. He's thriving. ... Ciarán is six now. He's the age that Cathal died. At the age of three, Cathal is completely paralyzed on that low-level plateau and right at the end. But Ciarán has grown to meet all the milestones. He has some nerve damage. He walks slowly, he kind of drags his feet a little. He wears splints on his lower legs. But other than that, he's absolutely fine, healthy, and thriving six-year-old boy. He's in his second year of primary school and doing really well."

"Both of my children... are fully physically and mentally able to carry on life as their 11- and 7-year-old peers. [Child's name] is a triplet and has two brothers who are her age and if anything, she is advanced ahead of her brothers in her physical and mental capabilities."<sup>18</sup>

[Child's name] is an extraordinary eleven-year-old, he's a future leader and entrepreneur. I'm I can look ahead and think of his future and where he's going to go."<sup>18</sup>

"Both the children are in mainstream school. They have an amazing group of friends that you wouldn't be able to tell that there was anything different to any of them. They are currently obsessed by The Greatest Showman and are always singing the songs at the top of their lungs."<sup>18</sup>

*"We watch [Child's name] play basketball in the pool with his brothers and he wrestles with his brothers, and he writes movie reviews for anyone who likes Adam Sandler. And this is all nine years after being diagnosed with MLD."*<sup>18</sup>

"My son is six and a half years post gene therapy, he was treated in December 2014, he is in full time mainstream education, and he doesn't require any additional support. He carries out the same activities

and completes the same school where his friends and peers to the same standard, he takes part in afterschool activities, such as swimming and Cubs. He is a typical 10-year-old child with the absolute best quality of life."<sup>18</sup>

"Our daughter is almost 9 years post diagnosis and she in an inspiration to many, making gifts on her own for charity and being the sister that she was born to be to her three brothers. She is in school thriving, and we get asked numerous times if she really has MLD. She would not be riding, swimming, playing, showering on her own, dressing on her own, singing in chorus and so on without Gene Therapy."<sup>18</sup>

## **Appendix 2: Table and Figures**

Table 1: Percentage of patients treated with arsa-cel classified as full or stable partial responders with	th
duration of follow-up of $\geq$ 5, 8 and 10 years.	

Duration of follow-up category, n (%)	Arsa-cel PS-LI (N=17)	Arsa-cel PS-EJ (N=8)	Arsa-cel ES-EJ (N=4)	Arsa-cel Pooled (N=29)
$\geq$ 5 years	12 (71%)	3 (38%)	2 (50%)	17 (59%)
$\geq 8$ years	5 (29%)	1 (13%)	2 (50%)	8 (28%)
$\geq 10$ years	5 (29%)	0%	0%	5 (17%)

# Table 2: Proportion of PS-LI and ES-EJ Partial Responders stabilizing by GMFC stage: Comparison of draft ICER model results to the arsa-cel clinical trial results.

GMFC Proportion of Partial		Proportion of Partial	Proportion of Partial	Proportion of Partial	
Stage	<b>Responders Stabilizing</b>	<b>Responders Stabilizing</b>	<b>Responders Stabilizing</b>	Responders Stabilizing	
	(PS-LI):	(PS-LI):	(ES-EJ):	(ES-EJ):	
	ICER Model	<b>Clinical Trial Data</b>	ICER Model	Clinical Trial Data	
0	3%	N/A	18%	N/A	
1	14%	63.6% (7/11)	50%	75% (3/4)	
2	20%	36.3% (4/11)	12%	0%	
3	24%	0%	9%	25% (1/4)	
4	19%	0%	5%	0%	
5	16%	0%	3%	0%	

Note: Percentages presented are based on stable partial responders only and do not include full responders or unstable partial responders.

# Table 3: Updated transition probabilities with impact on patient trace (PS-LI)

GMFC Stage	Natural History TPs Utilized (PS-LI): ICER Model	Stable Partial Responder clinical trial calibrated TPs (PS-LI)	Proportion of Partial Responders Stabilizing (PS-LI): ICER model with calibration*	Proportion of Partial Responders Stabilizing (PS-LI): Clinical Trial Data
0	73.86% =(EXP(-(1/3.3))	<mark>36.79%</mark> =(EXP(-(1/1))	<0.001%	N/A
1	76.32% =(EXP(-(1/3.7))	<mark>95.75%</mark> =(EXP(-(1/23))	63%	63.6% (7/11)
2	71.65% =(EXP(-(1/3.0))	<mark>99.00%</mark> =(EXP(-(1/100))	34%	36.3% (4/11)
3	71.65% =(EXP(-(1/3.0))	71.65% =(EXP(-(1/3.0))	<1%	0%
4	71.65% =(EXP(-(1/3.0))	71.65% =(EXP(-(1/3.0))	<1%	0%
5	90.11% =(EXP(-(1/9.6))	90.11% =(EXP(-(1/9.6))	<1%	0%

\*Estimated

# Table 4: Updated transition probabilities with impact on patient trace (ES-EJ)

GMFC Stage	Natural History TPs Utilized (ES-EJ): ICER Model	Stable Partial Responder clinical trial calibrated TPs (ES-EJ)	Proportion of Partial Responders Stabilizing (ES-EJ): ICER model with calibration*	Proportion of Partial Responders Stabilizing (ES-EJ): Clinical Trial Data	
0	89.91% =(EXP(-(1/9.4))	<mark>36.79%</mark> =(EXP(-(1/1))	<0.001%	N/A	

1	94.68%	<mark>97.33%</mark>	73%	75% (3/4)
	=(EXP(-(1/18.3))	<mark>=(EXP(-(1/37))</mark>		
2	79.67%	<mark>36.79%</mark>	3%	0%
	=(EXP(-(1/4.4))	<mark>=(EXP(-(1/1))</mark>		
3	79.67%	<mark>99.34%</mark>	21%	25% (1/4)
	=(EXP(-(1/4.4))	<mark>=(EXP(-(1/150))</mark>		
4	79.67%	79.67%	<1%	0%
	=(EXP(-(1/4.4))	=(EXP(-(1/4.4))		
5	96.45%	96.45%	<1%	0%
	=(EXP(-(1/9.6))	=(EXP(-(1/27.7))		

\*Estimated

### Table 5: Comparison of US MLD-specific utility scores with other rare, progressive and severe disease

### analogs

GMFC- MLD Stage	MLD* (LI)	MLD (EJ)	SMA (ICER values) <sup>4</sup>	SMA (Lloyd) ⁵	CLN-2 <sup>6</sup>	X-ALD <sup>7</sup>	DMD <sup>8</sup>	MPS IVa <sup>9</sup>
0	Gen Pop.	NC: Gen Pop. Cl: 0.75 Sl: 0.46	Gen Pop.	Gen Pop.	NC: 0.985 (CLN2 6)	Gen. Pop.	Gen. Pop.	Gen. Pop.
1	0.71	NC: 0.91 Cl: 0.63 Sl: 0.34		0.71 (Reclassified SMA 3)	NC: 0.762 MI: 0.629 (CLN2 4, 5)	0.68 (ALD-DRS I)	0.73 (Early Ambulatory)	0.54 (No wheelchair use)
2	0.44	NC: 0.84 Cl: 0.56 Sl: 0.27	0.6 (Sitting)	0.52 (Walks with assistance)	NC: 0.464 MI: 0.424 SI: 0.218 (CLN2 3, 2, 1)	0.59 (ALD-DRS II)	0.64 (Late Ambulatory)	0.41 (Some wheelchair use)
3	-0.04	NC: 0.38 Cl: 0.10 Sl: -0.11		-0.04 (Reclassified SMA 2)	SI: -0.163 (CLN2 0)	0.11 (ALD-DRS III)	0.21 (Early Non- ambulatory)	
4	-0.13	NC: 0.00 CI: -0.16 SI: -0.33			SI: -0.198 (CLN2 0 +VL)	0.03 (ALD-DRS IV)		0.08 (Wheelchair dependent)
5	-0.20	NC: -0.08 CI: -0.25 SI: -0.41	0.19 (Not Sitting; Permanent Ventilation)	-0.12 (SMA 1 Baseline)			0.18 (Late Non- ambulatory)	
6	-0.27	NC: -0.13 CI: -0.29 SI: -0.46		-0.33 (Requires ventilation)	SI: -0.211 (CLN2 0 +VL+PC)			

Rescaled utility scores from UK to US setting using US EQ-5d tariff. Note: Blank red boxes indicate utility scores that could not be mapped to the GMFC-MLD stages.

# Figure 1: Levels of ARSA enzyme in the PBMCs and CSF for one of the longest followed-up patients from the arsa-cel clinical trials





### Figure 2: Survival probability of n=54 and n= 51 Hurler Syndrome patients treated with HSCT









### References

<sup>6</sup> Brenner B, Henig I, Zuckerman T. Hematopoietic stem cell transplantation – 50 years of evolution and future perspectives. Rambam Maimonides Medical Journal; 2014 (5(4). https://ojrd.biomedcentral.com/articles/10.1186/s13023-020-01644-w

<sup>7</sup> Gardin A, Castelle M, Pichard S, Cano A et al. Long-term follow-up after haemopoietic stem cell transplantation for MPS1-H: a retrospective study of 51 patients. Bone Marrow Transplantation (2023) 58:295–302.

<sup>8</sup> Lum SH, Miller WP, Jones S, Poulton K, Ogden W, Lee H, Logan A, Bonney D, Lund TC, Orchard PJ, Wynn RF. Changes in the incidence, patterns and outcomes of graft failure following hematopoietic stem cell transplantation for Hurler syndrome. Bone Marrow Transplant. 2017 Jun;52(6):846-853.

<sup>9</sup> Patrick DL, Pearlman RA, Starks HE, Cain KC, Cole WG, Uhlmann RF. Validation of preferences for life-sustaining treatment: implications for advance care planning. Ann Intern Med. 1997;127(7):509-517.

<sup>10</sup> Ditto PH, Druley JA, Moore KA, Danks JH, Smucker WD. Fates worse than death: the role of valued life activities in healthstate evaluations. Health Psychol. 1996;15(5):332-343.

<sup>11</sup> Fried TR, Van Ness PH, Byers AL, Towle VR, O'Leary JR, Dubin JA. Changes in preferences for life-sustaining treatment among older persons with advanced illness.J Gen Intern Med. 2007;22(4):495-501.

<sup>12</sup> MLD PFDD. Externally-led patient focused drug development meeting held on October 21st, 2022. https://mldpfdd.org/
 <sup>13</sup> Bean K, Miller B, Jensen I, Fields C, Pang F. Evaluating the face validity of health state utility values (HSUVs) for MLD.
 Poster EE25 presented at ISPOR 2023, Boston, MA.

<sup>14</sup> Lo SH, Chang SC, Acaster S. Estimating utility values for health states in MLD. Value in Health. 2023.

<sup>15</sup> Auriemma C, O'Donnell H, Jones J, Barbati Z et al. Patient perspectives on states worse than death: a qualitative study with implications for patient centered outcomes and values elicitation. Palliative Medicine 2022; 36(2): 348-357.

<sup>16</sup> National Institute for Health and Care Excellence. Final evaluation determination: Elosulfase alfa for treating mucopolysaccharidosis type IVa [HST 2]. Final report. 2015.

<sup>17</sup> Hendriksz CJ, Lavery C, Coker M, Ucar SK, Jain M, Bell L, Lampe C. Burden of disease in patients with Morquio A syndrome: results from an international patient-reported outcomes survey. Orphanet J Rare Dis. 2014 Mar 7;9:32.

<sup>18</sup> NICE. Atidarsagene autotemcel for treating metachromatic leukodystrophy [ID1666]. Final Evaluation Determination Committee Papers. Page 23. Available at: https://www.nice.org.uk/guidance/hst18/evidence/final-evaluation-determination-committee-papers-pdf-11011940893

<sup>&</sup>lt;sup>1</sup>Beschle J, Döring M, Kehrer C, et al. Early clinical course after hematopoietic stem cell transplantation in children with juvenile metachromatic leukodystrophy. Mol Cell Pediatr 2020;7:12.

<sup>&</sup>lt;sup>2</sup> Martin S, Harris N, Romanus D. Evaluating meaningful changes in physical functioning and cognitive decline. *Journal of Patient-Reported Outcomes* (2023) 7:70.

<sup>&</sup>lt;sup>3</sup> Scala S, Basso-Ricci L, Dionisio F et al. Dynamics of genetically engineered hematopoietic stem and progenitor cells after autologous transplantation in humans. Nat Med. 2018;24(11):1683-1690.

<sup>&</sup>lt;sup>4</sup> Fumagalli F. Long-term clinical outcomes of atidarsagene autotemcel (autologous hematopoietic stem cell gene therapy [HSC-GT] for metachromatic leukodystrophy) with up to 11 years follow-up. Presented at WORLD Symposium 2023

<sup>&</sup>lt;sup>5</sup> Personal communication from Professor Robert Wynn to Orchard Therapeutics around the concept of durability of effect.



August 22, 2023

Dr. Steven D. Pearson President Institute for Clinical and Economic Review Two Liberty Square, Ninth Floor Boston, MA 02109

Dear Dr. Pearson.

The Partnership to Improve Patient Care (PIPC) appreciates the opportunity to comment on the Institute for Clinical and Economic Review (ICER) assessment of treatments for Metachromatic Leukodystrophy (MLD).

MLD is a rare hereditary disease for which there is no cure and very limited options for supportive care. MLD is a devastating disease, which leads to progressive nerve damage throughout the body and brain, eventually leading to early death for patients. Treatments for this rare disease are urgently needed, and it is imperative that ICER consider the rare patient population and severity of the disease in its assessment.

### QALYs are discriminatory and should not be used in value assessment.

Multiple studies have shown that cost-effectiveness models that use the quality-adjusted life year (QALY) discriminate against patients with chronic conditions<sup>1</sup> and people with disabilities.<sup>2</sup> There is widespread recognition that the use of the QALY is discriminatory. The QALY has historically been opposed by the American public and policy makers. The National Council on Disability (NCD), an independent federal agency, concluded in a 2019 report that QALYs discriminate by placing a lower value on treatments which extend the lives of people with chronic illnesses and disabilities. NCD recommended that policymakers and insurers reject QALYs as a method of measuring value for medical treatments.<sup>3</sup>

Traditional cost utility methods, like those ICER uses, often serve to undervalue treatments for highly severe illnesses. As a result, such studies may lead payers to underpay for treatment of severe illnesses, like MLD. ICER should be evolving away from use of the QALY, and, instead, measuring value based on the most up to date science and improved health utilities reflecting the value to the patient.<sup>4</sup>

### ICER should practice severity weighting, as is accepted by many other HTA bodies.

<sup>&</sup>lt;sup>1</sup> Paulden M. Recent amendments to NICE's value-based assessment of health technologies: implicitly inequitable?. Expert review of pharmacoeconomics & outcomes research. 2017 May 4;17(3):239-42.

<sup>&</sup>lt;sup>2</sup> Nord E, Pinto JL, Richardson J, Menzel P, Ubel P. Incorporating societal concerns for fairness in numerical valuations of health programmes. Health economics. 1999 Feb:8(1):25-39.

<sup>&</sup>lt;sup>3</sup> https://www.ncd.gov/sites/default/files/NCD\_Quality\_Adjusted\_Life\_Report\_508.pdf

<sup>&</sup>lt;sup>4</sup> MacKillop E, Sheard S. Quantifying life: understanding the history of quality-adjusted life-years (QALYs). Social Science & Medicine. 2018 Aug 1;211:359-66.



As PIPC has stated in past comments to ICER, it is imperative that it follow the model of other HTA organizations and incorporate severity weighting in its assessments. Non-linear utility function in costutility analysis has been widely accepted with the discipline of health economics and has been incorporated into value assessment methods globally. European countries such as Norway, Sweden, the Netherlands,<sup>5</sup> and most recently the UK's NICE,<sup>6</sup> are actively using information on severity of the disease in the question to better inform approval decisions for new medicines. These countries are addressing the problem by developing multiple thresholds specific to each disease.

MLD is a devastating disease, and based on the utilities ICER chooses to use in its model, most other HTA bodies would consider it a severe condition and adjust their thresholds. In the Netherlands it would be granted a threshold four times that used for less severe conditions.<sup>7</sup> In Norway it would be granted a threshold of three times that for less severe conditions.<sup>8</sup> PIPC urges ICER to familiarize itself with the latest developments in value assessment instead of remaining wedded to a traditional CEA, which is dated in many ways. This will enable ICER to conduct more accurate, sensitive assessments for patients.

### ICER continues to conduct premature assessments.

Once again, ICER is choosing to conduct this assessment at an early stage of our understanding of the treatment in question without all of the information available. Within this construct, ICER chooses to make overly conservative assumptions about the long-term value of the treatment in question and its impact on a specific set of outcomes. This type of premature and conservative assessment can be harmful to patients, painting a distorted picture of the relative value of a new technology.

ICER's premature assessment also leads it to raise questions about the durability of the treatment. Questions of durability of treatment of any new technology are common, but these should not be used to restrict access to patients who will benefit today. ICER states that long-term durability is unknown for arsa-cel in MLD, but there is up to 11 years of follow-up data in the LI-MLD patients<sup>9</sup> and up to 9 years in the EJ-MLD patients.<sup>10</sup> In both cases the Kaplan-Meier curves suggest quite considerable evidence for durability. It leaves us with the question as to what exactly is 'enough' evidence of durability in a novel drug that can reduce mortality by over 60% over ten years. The most problematic aspect of ICER's commentary on durability is that this reasoning assumes there is no downside to delaying access to new therapies, but this is far from true for patients waiting for treatments, especially those with few, if any, options. Every year this drug is not available for LI-MLD and EJ-MLD treatment, patient lives are

healthcare: severity, age, or both? Value Health. 2019;22(12):1441-1449.

<sup>&</sup>lt;sup>5</sup> Angelis A, Lange A, Kanavos P. Using health technology assessment to assess the value of new medicines: results of a systematic review and expert consultation across eight European countries. The European Journal of Health Economics. 2018 Jan 1;19(1):123-52. <sup>6</sup> Collins C, Cheng J, Taylor I, Mumford A. HTA73 Evaluation of NICE Severity Modifiers. Value in Health. 2022 Dec 1;25(12):S310.

<sup>&</sup>lt;sup>7</sup> Reckers-Droog V, van Exel J, BrouwerW. Equity weights for priority setting in

<sup>&</sup>lt;sup>8</sup> Magnussen J, Aaserud M, Granaas T, et al. På ramme alvor - Alvorlighet og prioritering. Government of Norway. https://www.regjeringen.no/contentassets/d5da48ca5d1a4b128c72fc5daa3b4fd8/summary\_the\_magnussen\_ report\_on\_severity.pdf.

<sup>&</sup>lt;sup>9</sup> Orchard Therapeutics. A Safety and Efficacy Study of Cryopreserved OTL-200 for Treatment of Metachromatic Leukodystrophy (MLD). Orchard Therapeutics. Clinicaltrials.gov Web site. https://classic.clinicaltrials.gov/ct2/show/NCT03392987. Published 2022. Accessed2023.

<sup>&</sup>lt;sup>10</sup> Fumagalli F, Calbi V, De Mattia F, et al. Long-term clinical outcomes of atidarsagene autotemcel (autologous hematopoietic stem cell gene therapy for metachromatic leukodystrophy) with up to 11 years follow-up. The San Raffaele Telethon Institute For Gene Therapy. 2023.



lost. Patient lives should not be ignored in order to suit a conservative view of what constitutes enough evidence.<sup>11</sup>

### ICER should use the societal perspective as the sole base case in this model.

MLD has an immense societal impact, including caregiver burden. Ignoring this reality has the potential to significantly exacerbate inequality within the disease state. The reality is that, given the immense caregiving needs of MLD, families are forced to make very difficult choices. Either the child's care and/or the family's earning potential may be compromised as a result. ICER has chosen to give equal weight to its healthcare perspective results that exclude caregiver utilities and indirect costs, which we believe is a mistake. For some diseases the burden on caregivers and the impact on social care costs make the societal perspective a more relevant choice than the health care perspective. NICE, which ICER leans heavily on for its approach to value assessment, has already included caregiver utility in its cost-effectiveness models for diseases such as Alzheimer's, MS and Parkinson's disease.<sup>12</sup> It is also the recommended perspective for cost-effectiveness models of the 2<sup>nd</sup> panel on cost-effectiveness<sup>13</sup>, and ISPOR.<sup>14</sup>

In addition, the source for the caregiver dis-utilities were from a source that evaluated a different disease, neuronal ceroid lipofuscinosis type 2,<sup>15</sup> and they show no gradation from GMFC health state 2 to GMFC health state 6. This is not an accurate source for these utilities as the level of care required, and the resulting impact on a caregivers' quality of life across these states of disease would be considerably different. ICER shares in the assessment that it was given a set of caregiver utilities directly by the manufacturer that does indeed vary by GMFC state. PIPC would recommend using that source for caregiver utilities.

### ICER should factor system effects into its assessment.

The availability of a treatment for MLD changes the diagnostic and screening landscape for the disease. It means that patients are more likely to find an effective treatment, but it also triggers system effects.<sup>16</sup> In other words, the existence of the treatment leads to patients (and parents) having access to diagnostic certainty at an early stage of disease, cutting out the significant pathways of misdiagnosis and harmful and ineffective treatment strategies which can worsen the feelings of helplessness, anxiety and stress for

https://www.nice.org.uk/guidance/hst12. Published 2019. Accessed August 1, 2023

<sup>&</sup>lt;sup>11</sup> Stevens W, Philipson T, Wu Y, Chen C, Lakdawalla D. A cost-benefit analysis of using evidence of effectiveness in terms of progression free survival in making reimbursement decisions on new cancer therapies. InForum for Health Economics and Policy. 2014 Jan 1, 17(1);21-52.

<sup>&</sup>lt;sup>12</sup> Afentou N, Jarl J, Gerdtham UG, Saha S. Economic evaluation of interventions in Parkinson's disease: a systematic literature review. Movement disorders clinical practice. 2019 Apr;6(4):282-90.

<sup>&</sup>lt;sup>13</sup> Sanders GD, Neumann PJ, Basu A, Brock DW, Feeny D, Krahn M, Kuntz KM, Meltzer DO, Owens DK, Prosser LA, Salomon JA. Recommendations for conduct, methodological practices, and reporting of cost-effectiveness analyses: second panel on cost-effectiveness in health and medicine. Jama. 2016 Sep 13;316(10):1093-103.

<sup>&</sup>lt;sup>14</sup> Garrison Jr LP, Mansley EC, Abbott III TA, Bresnahan BW, Hay JW, Smeeding J. Good research practices for measuring drug costs in cost-effectiveness analyses: a societal perspective: the ispor drug cost task force report—Part II. Value in Health. 2010 Jan;13(1):8-13. <sup>15</sup> National Institute for Health and Care Excellence. Cerliponase alfa for treating neuronal ceroid lipofuscinosis type 2.

<sup>&</sup>lt;sup>16</sup> Jena AB, Stevens W, Gonzalez YS, Marx SE, Juday T, Lakdawalla DN, Philipson TJ. The wider public health value of HCV treatment accrued by liver transplant recipients. The American journal of managed care. 2016 May;22(6 Spec No.):SP212-9.



patient and family. These effects are not incorporated into the value of new innovations in standard QALY-based cost-utility models. They have a huge impact on patients' and caregivers' quality of life and on the efficiency of healthcare resource use more generally. In cases like MLD, PIPC would recommend system effects be incorporated into ICER's modeling.

### Conclusion

PIPC urges ICER to reconsider the use of the QALY and several of its modeling choices given the severity of and population impacted by MLD.

Sincerely,

T\_ Coelho

Tony Coelho Chairman Partnership to Improve Patient Care