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Atidarsagene autotemcel for treating metachromatic leukodystrophy [ID1666]

The following documents are made available to the consultees and commentators:

1. **Response to consultee, commentator and public comments on the Evaluation Consultation Document (ECD)**

2. **Company response to the Evaluation Consultation Document (ECD)**
   - Company response

3. **Consultee and commentator comments on the Evaluation Consultation Document** from:
   - ArchAngel MLD Trust
   - MLD Support Association UK
   - Mucopolysaccharide Society

4. **Comments on the Evaluation Consultation Document from experts:**
   - **Prof. Paul Gissen – clinical expert**, nominated by Orchard Therapeutics
   - **Dr James Davison – clinical expert**, nominated by MLD Support Association UK
   - **Nicola Elson – patient expert**, nominated by ArchAngel MLD Trust, MLD Support Association UK and The MPS Society

5. **Comments on the Evaluation Consultation Document received through the NICE website**

6. **Evidence Review Group critique of the company response**

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

OTL-200 for treating metachromatic leukodystrophy [ID1666]

Company response to the ECD

Orchard Therapeutics welcomes the opportunity to comment on the Evaluation Consultation Document (ECD) prepared by the HST Committee for the evaluation of OTL-200 for the treatment of early onset metachromatic leukodystrophy.

Orchard Therapeutics welcomes the recognition of the innovative status of OTL-200 by the HST Committee and their acknowledgement that it represents a step change in the management of MLD disease with the potential for substantial health and quality-of-life benefits compared to current management approaches.

Orchard Therapeutics also acknowledges the committee's feedback that despite being a suitable framework for decision making, the economic analysis does not capture all of the benefits of OTL-200. As such we have presented additional scenarios which attempt to capture some of these additional benefits. Whilst we acknowledge that quantification of these benefits may be challenging, these scenarios provide plausible insights on what the cost-effectiveness estimates could be if these benefits are taken into consideration.

Orchard Therapeutics is however concerned and disappointed by the Committee's provisional recommendations and considers them not to be a sound or suitable basis for guidance on the use of OTL-200 in the context of national commissioning by NHS England for the reasons detailed below. These points are further elaborated on in section 2 of this document.

Section 1

1.1 The conclusions on durability of motor and cognitive effect significantly underestimates the potential long-term benefits for OTL-200. 30 – 50 years is a more appropriate estimate

- The suggestion that the most plausible range of disease stabilisation in full and partial responders (stabilisers) is between 10 to 20 years (15 years on average) significantly underestimates the potential long-term outcomes for OTL-200 and in Orchard Therapeutics' view is not an accurate interpretation of the available evidence.
- Whilst the company acknowledges that without longer term data it is challenging to accurately predict the durability of effect, the following reasons provide a clinically plausible rationale for a much longer period of disease stabilisation than the arbitrary 10-to-20-year time frame chosen by the committee:
  - The established mechanism of action of OTL-200 (as acknowledged by NICE in the ECD (section 3.1)), indicates that OTL-200 effects are potentially lifelong.
  - Expert clinical opinion, from decades of successful treatment with allogeneic haematopoietic stem cell transplantation (allo-HSCT), indicates that once the transplanted haematopoietic stem and progenitor cells (HSPCs) successfully engraft in the patient, they and their progenies stably release functional enzyme throughout the patient's lifetime, and provide durable and clinically meaningful outcomes for patients (Personal Communication - UK transplant clinical expert, Lum et al 2017, Noh and Lee 2014, Taylor et al 2019). *Ex vivo* autologous gene therapy, including OTL-200, leverages the same durable qualities of HSPCs, and hence once engrafted, the potential for lifelong effect is shared across allo-HSCT and OTL-200.

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- OTL-200 demonstrates successful engraftment, with stable cellular reconstitution, evidenced by stable Vector copy number (VCN), accompanied by durable physiological and supraphysiological functional enzyme expression at the cellular level throughout follow up, as evidenced by stable **PBMC** ARSA enzyme expression.
- Patients with neurometabolic disorders, such as MPS, treated with allo-HSCT over 30 years ago and who had successful initial engraftment, continue to show disease stabilisation (Personal Communication, UK transplant clinical expert, Lum et al 2017).
- In addition, patients treated with Strimvelis (another *ex-vivo* gene therapy utilising the durable HSPC platform) continue to show disease stabilisation over 20 years after treatment.
- There is no plausible reason why the clinical effects of OTL-200 treated patients would be less durable than that of allo-HSCT or other similar HSPC technologies, especially as clinical results have shown that OTL-200 patients have stable engraftment throughout the follow-up period.

– The updated OTL-200 clinical data (with follow-up of up to 8 years) provided to NICE indicates that all the full responders and partial responders (stabilisers) remained stable or continued to improve throughout the follow-up period. The only patients who experienced declines were the unstable partial responders, who Orchard have always stated would progress, but at a slower rate than untreated natural history patients. Declines in these patients are considered to be related to the clinical status of the patient at initiation of treatment, rather than a loss of engraftment or loss of efficacy of the OTL-200 treatment itself.

1.2 The narrative that declines in cerebrospinal fluid ARSA enzyme in OTL-200 treated patients indicates a potential waning of clinical effect and loss of disease stabilisation, is an extremely pessimistic interpretation of the clinical data and not supported by established clinical opinion.

- Whilst the concerns that NICE raised regarding the apparent declines in the cerebrospinal (CSF) ARSA enzyme levels in some patients are understood, the company does not believe that this has implications on long term clinical outcomes for the following reasons:

  – Clinical experts at the committee meeting have stated that the values seen in treated OTL-200 patients are not of clinical concern or clinical relevance, as they may represent normal fluctuations in CSF enzyme levels. Additionally, CSF enzyme levels, including ARSA levels, are not routinely monitored in clinical practice, as they are not considered to be important in monitoring patient progress or outcomes. CSF enzyme levels are measured in the investigational clinical trial setting to establish that the enzyme is found beyond the blood brain barrier, however this measurement is not used as a direct surrogate marker for efficacy. In clinical practice a holistic view of the patient picture is used, including MRI, as well as assessments such as motor function and cognition. Peripheral blood enzyme testing and VCN are adequate outcomes to confirm that engraftment is stable and maintained.

  – Clinical opinion is that ARSA CSF enzyme levels do not correlate with clinical outcomes. In fact, clinical outcomes in patients with ARSA CSF enzyme below 0.31 nmol/mg/h (lower level of normal in normal paediatric population) were similar to

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outcomes in patients above this level. In addition, none of the patients who had levels consistently below or around 0.31 nmol/mg/h had a worsening of clinical outcomes over their follow up (see section 2.2).

- Emerging evidence indicates that in the general population, ARSA-CSF enzyme levels in adults (mean levels [0.305 nmol/mg/h]; range [0.12 – 0.54 nmol/mg/h]) are generally lower than that of children (mean levels [1.039 nmol/mg/h]; range [0.31 – 2.82 nmol/mg/h]), and healthy children may have values lower than the lower limit of normal for children (i.e. less than 0.31 nmol/mg/h) (Morena et al 2021). These findings show that a range of ARSA levels in CSF is a normal physiological occurrence and is not a result of loss of engraftment as suggested by the ERG.
- Due to the anatomy and physiology of the brain, enzyme levels in the CSF may be a fraction of the brain tissue levels, where enzyme is released by corrected microglia, deep within the cerebrum, into the interstitial space between the cells, of which most is likely absorbed by nearby cells and only a proportion will end up in the CSF. As such the level in the CSF is not an accurate estimation of the amount of enzyme that resides in and is available to brain cells (see section 2.2. for further details).

- Finally, clinical opinion from transplant experts with several decades of experience using HSCT to treat metabolic disorders, is that as long as engrafted cells remain in the body, there would continue to be a steady release of functional enzyme. VCN results from the updated clinical data provide evidence of stable and persistent engraftment levels throughout the follow-up period without any decrease.

1.3 The clinical benefits of treating patients with OTL-200 in the ES-EJ subgroup have been significantly underestimated.

- Orchard Therapeutics believes the HST Committee's preferred assumptions result in a significant underestimation of the benefits of OTL-200 for early symptomatic early juvenile (ES-EJ) patients.
  - Specifically, whilst the clinical outcomes in ES-EJ patients may not be as profound as those in pre-symptomatic patients relative to current standard of care, these benefits are still substantial and meaningful even when patients are stabilised at the higher GMFC-MLD scores of 3 and 4.
  - In addition, the narrative that patients who stabilise at GMFC 3 and 4 would have a poor quality of life does not align with patient group feedback and clinical expert opinion which indicates these patients have a good quality of life. This is demonstrated by their abilities to attend mainstream school, enjoy hobbies, acquire new skills, have freedom from feeding complications and retain the ability to communicate and socialise. Unfortunately, it has not been possible to capture these in the health economic analysis given the challenge of measuring these in clinical trials, and these benefits not being included in the vignettes from the utility study. However these benefits been reported in patient survey results included in the committee papers for the 1st committee meeting

1.4 ES-EJ patients represent a small and shrinking proportion of patients eligible for OTL-200. The cost-effectiveness of OTL-200 would hence increase over time

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- Orchard Therapeutics acknowledges the HST Committee's concerns about the uncertainty regarding the proportion of ES-EJ patients, however epidemiological evidence and clinical / patient group data spanning over 20 years indicates that the proportion of ES-EJ patients would be small, representing less than 15% of all eligible OTL-200 patients which would translate to less than 1 patient every other year in England and Wales.
- Over time, due to improvements in diagnosis facilitated by increased disease awareness and genomic testing in the short term as well as the introduction of newborn screening in the longer term, the proportion of ES-EJ patients would decrease as more patients are identified at a pre-symptomatic stage. Treatment of these patients at an earlier stage (i.e. GMFC 0 and normal cognition) would be expected to translate into improved clinical outcomes as indicated by the clinical trial results for the pre-symptomatic patients.

1.5 The decision not to use 1.5% discount rate for OTL-200 is inconsistent with NICE HST interim method's guide and NICE HST decisions in previous appraisals of other gene therapies.

- While Orchard Therapeutics acknowledges some patients treated with OTL-200 may have experienced some disease progression (albeit at a slower rate than untreated patients) and stabilise at worse health states than other treated patients (i.e. ES-EJ patients who already have disease symptoms at the point of treatment), the company believes that for pre-symptomatic patients the 1.5% discount rate is appropriate for decision making, as these patients have the potential to live in full or near full health for over 30 years.
- Based on NICE preferred assumptions, 50% of late infantile and 75% of PS-EJ patients would stabilise at GMFC 0 or 1 with normal cognitive function. These patients would have full or near full health given their utility values of 0.90 or greater. A further 17% of LI patients are assumed to stabilise at GMFC 2 with normal cognitive function (utility value of 0.80), which can be argued to also be near full health given their high quality of life.
- Although the case for 1.5% discount rate for ES-EJ may be less clear than for the pre-symptomatic patients, it should be noted that ES-EJ currently accounts for a small proportion of eligible patients (estimated less than 15%), and over time this proportion would be expected to further decline given earlier diagnosis.
- Finally, in the evaluation of Zolgensma and Luxturna, despite the HST committee identifying uncertainties in the long-term outcomes, a 1.5% discount rate was accepted for decision-making based on the view that a proportion of patients had the potential to have life-long disease stabilisation. Orchard Therapeutics believes the clinical evidence provided for OTL-200 with a duration of follow-up which is comparable or longer than either of these gene therapies should provide confidence that OTL-200 is also eligible to fulfil this criteria despite the uncertainties raised by the committee.

Finally, Orchard Therapeutics would like to clarify that it did not accept the ERG's preferred assumptions or corrections after the 1st HST Committee meeting as stated in section 4.16 of the ECD. Rather in the interest of pragmatism and facilitating easier decision-making by the committee, the company decided not to contest these assumptions especially as the impact on the ICER was negligible. The company's desire to facilitate decision making may have been misinterpreted as a concession and acceptance of all of the ERG's comments, which is not the case.

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Section 2 of this response provides further supporting evidence for the long-term durability of treatment effect as well as the results of alternative scenarios (integrating some of NICE preferred assumptions) for the committee's consideration

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Section 2

2.1. Long term outcomes of OTL-200

Orchard Therapeutics believes that the HST Committee's conclusion that the "most plausible range of disease stabilisation is between 10 and 20 years" represents a very conservative interpretation of the clinical evidence in section 4.18. These interpretations include:

i. *"…the additional 2 years of data from the company's updated data cut showed that some patients' motor function declined even after periods of apparent stabilisation (2 to 3 years)".* This is misleading for several reasons:

- Orchard Therapeutics believes that the definition of apparent disease stabilisation may have been based only on GMFC-MLD score. While Orchard Therapeutics acknowledge this approach was used in the original submission as a practical way of modelling disease progression given the difficulties of using multiple measures, Orchard Therapeutics believes that in line with the discussions at the committee meetings on 15th April and 10th June 2021, disease stabilisation should be defined based on the company's revised definition which is based on a broader set of clinical outcomes including GMFC, GMFM total score (a more multidimensional motor score), DQp and MRI total score. This broader and more holistic approach to the analysis of clinical outcomes was taken due to feedback from expert clinicians, and the committee during the 15th April committee meeting and was the basis for the updated classification used in our response to the ERG addendum (see Table B2) submitted on 24th May. Importantly, Orchard Therapeutics notes the statement in section 4.11 of the ECD *"the committee considered that the company's revised classification, taking account of other outcomes besides GMFC-MLD, was the most appropriate for decision making"*.

- Orchard Therapeutics maintains that the evidence supports that no patient experienced disease progression after a 2 to 3-year period of apparent disease stabilisation. These patients were either not stable during the 2 to 3-year period the ERG referred to (Group 1),or were stable during this period and remained so afterwards (Group 2). Further exploration of these groups is provided below. The statement by the ERG is thought to be due to the ERG defining stabilisation based on GMFC-MLD score only, before the revised approach provided a more holistic outcome assessment, as discussed above.

  - **Group 1 patients:** As can be seen in the updated provided as part of Orchard's response to the ERG Addendum report (pages 231 - 232, 236 and 239 of Appendix A_latest_data_analysis_2021.pdf), most of the patients [redacted] The GMFM is a more sensitive scale compared to GMFC-MLD and more closely reflective of the overall clinical picture.

  - **Group 2 patients**: [redacted] Given the stable GMFM total score and other clinical outcomes, characterising this patient as having a decline in motor function or any form of disease progression does not align with the clinical evidence as per the revised classification, and further illustrates why a more holistic assessment of these patients is the best representation of a stable and durable response.

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ii. *"…the number of patients whose symptoms were no longer stable had increased in between data cuts."* The company disagrees with this interpretation of the updated clinical data presented:

- Orchard Therapeutics' updated data cut showed continued disease stabilisation in patients classified as full responders (Figure 1) or partial responder (stabilisers) (Figure 2). The only patients who continued to decline were the unstable partial responders (Figure 3)

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Figure 1: Means and standard error (SE) for clinical outcome measures and disease markers (i) GMFM, (ii) Development Quotient performance [DQp]) (iii) MRI (iv) median and interquartile range for GMFC MLD, for all full responders [LI and PS-EJ].

These results show broad disease stabilisation throughout the follow-up period for full responders. (Preliminary figures based on a December 2019 Data Cut).

[redacted]

Figure 2: Means and standard error for clinical outcome and disease markers (i) GMFM, (ii) Development Quotient performance [DQp]) (iii) MRI (iv) median and interquartile range for GMFC MLD, for all Stabilised Partial responders [LI and ES-EJ].

These results show stable partial responders experience disease stabilisation throughout the follow-up period, albeit with some level of motor impairment. (Preliminary figures based on a December 2019 Data Cut).

[redacted]

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Figure 3: Means and standard error for clinical outcome and disease markers (i) GMFM, (ii) Development Quotient performance [DQp]) (iii) MRI (iv) median and interquartile range for GMFC MLD, for all Unstable Partial responders [LI, PS-EJ and ES-EJ].

These results show unstable partial responders experience continued and consistent declines across clinical outcomes (Preliminary figures based on December 2019 Data Cut). However, this is at a slower rate compared to natural history patients (data not shown).

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2.2. ARSA enzyme in CSF of OTL-200 treated patients

The narrative that declines in cerebrospinal fluid (CSF) ARSA enzyme in OTL-200 treated patients indicates a potential waning of clinical effect and loss of disease stabilisation, is not plausible nor supported by established clinical opinion for a number of reasons stated above, but to reiterate:

i. Firstly, not all patients had a continued decline in CSF ARSA enzyme as implied in the ECD. In fact, PS-EJ and ES-EJ patients with available data showed stable CSF ARSA enzyme with no decline (Figure 4) throughout the follow-up period. Only some LI patients (n = 3) saw a decline in CSF ARSA enzyme levels.

Figure 4: ARSA Activity Profiles in CSF (nmol/mg/h) Geometric Means and 95% Confidence Intervals (Dec 2019 data cut, n = 17)

ii. Secondly, as mentioned in section 1.2, the "apparent declines" seen in LI patients may represent a normal physiological occurrence as shown by the lower normal enzyme levels for adults compared to paediatric population (Table 1).

Table 1: CSF ARSA activity (in nmol/mg/h) for paediatric and adult healthy samples (Source Morena et al 2021).

	Pediatric CSF ARSA (nmol/mg/h)	Adult CSF ARSA (nmol/mg/h)
N	33*	8*
Minimum	0.31	0.12
25th percentile	0.83	0.25
Median	1.00	0.32
75th percentile	1.67	0.41
Maximum	2.82	0.54
Geometric mean	1.039	0.305
95% range	0.859–1.258	0.214–0.435

iii. In addition, the lower level of normal (0.31 nmol/mg/h) quoted in Morena et al 2021, which has been used by Orchard Therapeutics, is for children. CSF ARSA values below this level have been observed in a healthy child sample, and in adults (see Figure 5).

Figure 5: ARSA activity in CSF of paediatric and adult healthy donors. E) ARSA activity. F) Geometric mean and interquartile range of ARSA activity (Source Morena et al 2021). "red marked +" indicates sample not included on the estimation of normal range of ARSA activity in CSF

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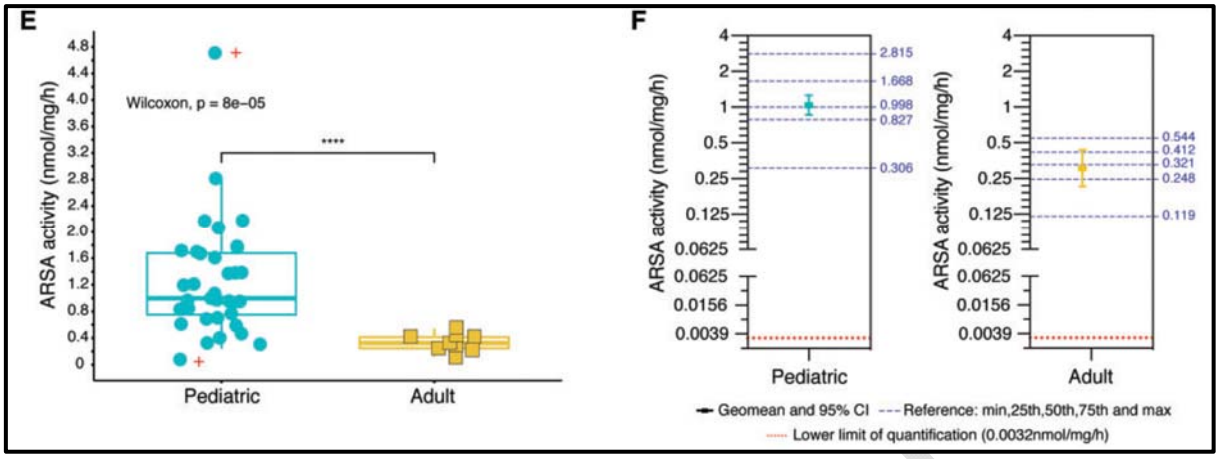

Furthermore, as stated in section 1, clinical opinion is that ARSA CSF enzyme levels do not correlate with clinical outcomes. This view is supported by the results of a recent analysis of the clinical trial data undertaken by Orchard therapeutics which showed there was no correlation between CSF ARSA enzyme levels and clinical outcomes (GMFM total score, GMFC-MLD score, DQp) and MRI total score (Figure 6 below) at the corresponding time point. Of great relevance, of the treated patients with ARSA CSF enzyme below 0.31 nmol/mg/h (lower level of normal in paediatric population), the majority had normal cognitive function (DQp ≥ 85) and moderate to excellent gross motor function (GMFM total score ≥ 60%) at the corresponding time point (red box in Figure 6). In addition, none of the patients who had levels consistently below or around 0.31 nmol/mg/h had a worsening of clinical outcomes over their follow up further supporting the importance of focus on the holistic assessment of clinical outcomes instead of CSF ARSA enzyme levels as a proxy indicator of efficacy.

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Figure 6: ARSA activity in CSF and corresponding (i) GMFM Total Score (ii) Development Quotient (performance) score (iii) MRI (iv) and GMFC at the same visits. Red rectangle indicates GMFM, DQp MRI and GMFC-MLD scores at ARSA CSF values lower normal limit (0.31 nmol/mg/h) for children

These results demonstrate that there is no clear association between CSF ARSA enzyme levels, and clinical outcomes (as measured by GMFM, GMFC, DQp and MRI) at the same time point. Patients with CSF ARSA values <0.31 nmol/mg/h have similar clinical outcomes compared to those with higher ARSA CSF values.

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iv. As mentioned in section 1, due to the anatomy of the brain, ARSA enzyme levels in the CSF may be a fraction of brain tissue levels, mainly because in this treatment ARSA enzyme is released by the corrected microglia cells deep within the cerebrum into the interstitial space between the cells, of which most is likely absorbed by nearby cells and only a proportion will end up in the CSF. It should be noted that the defective cells resulting in MLD disease (e.g. neurons and oligodendrocytes) are not in direct contact with the CSF. Rather the cells which are in direct contact with the CSF are the ependymal cells of the ventricles (Nakada and Kwee 2018). These cells are not of haematopoetic origin, and therefore will not contain a functioning copy of the ARSA gene in an OTL-200 treated patient. As these cells do not take part in myelin metabolism, they are not involved in the demyelination seen in MLD, and hence do not require functional correction for efficacious treatment of the disease. All of these points provide a biological rationale for why making a direct correlation between intracerebral and CSF levels of an enzyme is unreliable.

Finally, to align with clinical practice, the company believes any characterisation of disease progression should be based on holistic assessment of multiple clinical outcomes. As such, a patient showing stabilisation or improvement across all clinical outcomes (see Figure 7 below) should be characterised as stable even if the CSF ARSA enzyme levels appear to decline in that time period for the reasons previously mentioned. Conversely a patient seeing decline in majority of the clinical outcomes (Figure 8 below) is a patient clearly deteriorating irrespective of their CSF ARSA enzyme levels. Whilst the company acknowledges that patients could experience decline in motor function and stabilisation in cognitive function, given the reasons mentioned above, a slight reduction in GMFM and/or GMFC-MLD score should not be characterised as disease progression except it if is clinically significant (i.e. ≥ 10% decrease in GMFM total score) and/or accompanied by increase in MRI total score (which as per clinical feedback is a marker of CNS deterioration).

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Figure 7: Exemplar of a stable patient. Clinical outcomes and disease markers (MRI, DQ performance, NCV, GMFM, GMFC-MLD) are stable or improving over the follow-up period, despite declining ARSA-CSF enzyme levels. (December 2019 Data Cut).

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Figure 8: Exemplar of an unstable responder. Clinical outcomes and disease markers (MRI, DQ performance, NCV, GMFM, GMFC-MLD) are worsening over the follow-up period, despite stable enzyme levels (ARSA-CSF, ARSA-PBMC, ARSA-BM). (December 2019 Data Cut).

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2.3 Updates to the Economic Analysis

Although Orchard Therapeutics maintains that its alternative base case presented in the response to the ERG addendum is the most plausible reflection of the evidence base, the company has updated this to include some of the preferred assumptions of the HST Committee in order to facilitate decision-making. A list of changes made to the HST Committee's preferred set of assumptions are summarised in the table below (Table 2). For transparency the NICE preferred scenarios are highlighted in light green.

Table 2: Assumptions underpinning company base case

Parameter	Updated Company Base Case	Comments
Utility Score	NICE preferred assumptions.	▪ The company accepts NICE's preference to use the rescaled utility set. ▪ However, the company presents a scenario in which a notary top-up of 0.1 is included to OTL-200 patients to capture some of the additional treatment related benefits beyond cognitive and motor function[1]
Disease stabilisation	50 years	▪ The company disagrees with NICE's estimation of 10 -20 years for disease stabilisation for the reasons mentioned in section 1 and 2.1. ▪ Whilst we believe response would be durable and lifelong, we recognise that HSCT only became a viable treatment option in other diseases 50 years ago, as such durability beyond 50 years is unknown (Henig and Zukermen 2014). ▪ A scenario analysis looking at 30 years, which represents the maximum follow-up to date of transplanted rare metabolic disease patients, is also modelled.
Progression Modifier (only changed ES-EJ)	LI progression modifiers for EJ subgroups with minor change ▪ PM of GMFC-MLD 0 to 1, reset to 1.0	▪ The company accepts NICE's decision to use the LI progression modifiers for PS-EJ and ES-EJ subgroups. ▪ However, the company maintains that it is clinically implausible that treatment would accelerate disease progression at any stage. Hence the progression modifier for GMFC-MLD 0 to 1, should not be less than 1.0 and as such has been reset to 1.0
Response rate classification	o **NICE preferred assumption**	▪ Note although the updated data cut also supports the company's response rate classification for LI patients, given it had only 8 out of 15 treated LI patients, the company has pragmatically adopted the ERG's classification for LI patients as it is more conservative
Subgroup distribution		▪ ERG Base Case
Discount rate	▪ **PS-LI and PS-EJ:** 1.5% and 3.5% ▪ **ES-EJ:** 3.5%	▪ 1.5% is a suitable basis for decision making for pre-symptomatic patients as the majority of these patients would be stabilised at GMFC-MLD 0 or 1 for long periods and retain normal cognitive function (high level of quality of life), and as such have full or near full health (see section 1).

[1] Additional benefits reported by caregivers include freedom of feeding complications which may require PEG insertion, reduction in painful muscle spasms, improved peripheral neuropathy. To date none of the treated patient have had PEG insertion compared to most natural history patients who would have it at some point between GMFC 3 and 5. Also the clinical data shows better NCV values for treated patients compared to NH patients which would translate into reduction in peripheral neuropathy

Caregiver disutility	NICE preferred assumptions.	▪ Whilst the company's base case includes the caregiver disutility, the company would like to highlight that the NICE preferred assumptions result in a situation where in health states GMFC MLD 4 -6, the caregiver disutility exceeds the patient's utility leading to net negative utility on the family level. ▪ The company doesn't believe this should be the case for health states with positive utility. Also, there is a plausible argument the disutility would not be constant throughout the patient's life[2] ▪ For these reasons, the company presents an alternative scenario not including caregiver disutility

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[2] The original model assumed that caregivers of MLD patients in GMFC-MLD 5 and 6 health states would have a disutility. For simplification purposes, this disutility was modelled to last for the whole 100 year time horizon of the model, as using this duration for the disutility compared to a shorter duration (e.g. till patient attained adulthood) had a negligible impact on the ICER. However with the NICE preferred assumptions (that the caregiver disutility would apply to GMFC MLD 1 – 6 health states), inclusion of the caregiver disutility significantly worsens the ICERs and QALY for ES-EJ patients. This is because for each year spent in GMFC 4 to 6 health state, the caregiver disutility (-0.216) is greater than the utility of that health state [redacted] resulting in a net negative family utility. **The company believes that for health states with positive utilities, the net family utility should be at worse 0 (i.e. caregiver disutility should not exceed patient utility).** In addition, there is a plausible argument that the caregiver disutility would not remain at the same level throughout the life of patient treated with gene therapy, given the life-expectancy of the parents, and also as the physical and psychological burden of caregiving which would be less in adulthood (where the patient is cared for in long term care facilities) compared to childhood. As such the company has provided a scenario without the caregiver disutility.

Table 3: Updated Company Scenario Analysis (1.5% discount rate)

Scenario	PS Late Infantile				PS Early Juvenile				ES Early Juvenile				Pooled			
	Costs (£)	QALY	Und QALY	ICER	Costs (£)	QALY	Und QALY	ICER	Costs (£)	QALY	Und QALY	ICER	Costs (£)	QALY	Und QALY	ICER
Updated Company Base Case																
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OTL-200	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 1: Utility Top-Up																
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OTL-200	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 2: No caregiver disutility																
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OTL-200	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 3: 30 years disease stabilisation																
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OTL-200	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 4: Lifetime disease stabilisation																
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OTL-200	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 5: Utility Top-up + 30 years disease stabilisation																
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OTL-200	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 6: Utility Top up + Lifetime disease stabilisation																
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OTL-200	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 7: Utility top-up + No-Caregiver disutility																

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Scenario	PS Late Infantile				PS Early Juvenile				ES Early Juvenile				Pooled			
	Costs (£)	QALY	Und QALY	ICER	Costs (£)	QALY	Und QALY	ICER	Costs (£)	QALY	Und QALY	ICER	Costs (£)	QALY	Und QALY	ICER
BSC	[redacted]															
OTL-200	[redacted]															
Scenario 8: Utility Top-up + No caregiver disutility + 30 years disease stabilisation																
BSC	[redacted]															
OTL-200	[redacted]															
Scenario 9: Utility Top up + No-caregiver disutility + Lifetime disease stabilisation																
BSC	[redacted]															
OTL-200	[redacted]															

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Table 4: Updated Company Scenario Analysis (3.5% discount rate)

Scenario	PS Late Infantile				PS Early Juvenile				ES Early Juvenile				Pooled			
	Costs (£)	QALY	Und QALY	ICER	Costs (£)	QALY	Und QALY	ICER	Costs (£)	QALY	Und QALY	ICER	Costs (£)	QALY	Und QALY	ICER
Updated Company Base Case																
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OTL-200	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 1: Utility Top-Up																
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OTL-200	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 2: No caregiver disutility																
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OTL-200	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 3: 30 years disease stabilisation																
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OTL-200	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 4: Lifetime disease stabilisation																
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OTL-200	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 5: Utility Top-up + 30 years disease stabilisation																
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OTL-200	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 6: Utility Top up + Lifetime disease stabilisation																
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OTL-200	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 7: Utility top-up + No-Caregiver disutility																
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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Scenario	PS Late Infantile				PS Early Juvenile				ES Early Juvenile				Pooled			
	Costs (£)	QALY	Und QALY	ICER	Costs (£)	QALY	Und QALY	ICER	Costs (£)	QALY	Und QALY	ICER	Costs (£)	QALY	Und QALY	ICER
OTL-200	[redacted]															
Scenario 8: Utility Top-up + No caregiver disutility + 30 years disease stabilisation																
BSC	[redacted]															
OTL-200	[redacted]															
Scenario 9: Utility Top up + No-caregiver disutility + Lifetime disease stabilisation																
BSC	[redacted]															
OTL-200	[redacted]															

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OTL-200 for treating metachromatic leukodystrophy [ID1666]

Consultation on the evaluation consultation document – deadline for comments 5pm on Friday 30 July 2021 - email: NICE DOCS

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Evaluation Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	**ArchAngel MLD Trust**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**N/A**

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Name of commentator person completing form:	[redacted]
Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	**Has all of the relevant evidence been taken into account?** We appreciate that the previously submitted evidence based on the UK clinical experience of MLD and UK cohort of treated patients is limited due to the very small size of the affected population. We have therefore consulted with a number of esteemed clinical experts and patient organisations world-wide who have direct experience of MLD patients, both untreated and treated with OTL-200, in order to verify that UK experience is consistent with their own experience and observations. We have received written testimonies from the following (also submitted to NICE): [redacted] • *Cure MLD*: a non-profit organisation which supports MLD research and which has helped 16 children access gene therapy in Milan • *MLD Foundation*: a global organisation which supports MLD families and patients and connects MLD researchers and clinicians in the pursuit of treatments and newborn screening • *Hunter's Hope Foundation:* a charity serving hundreds of Leukodystrophy families across the world including many families affected by MLD

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	We have also undertaken additional research (in conjunction with The MPS Society and MLD Support UK) in conducting a survey of treated families from around the globe for further consideration by the committee. NB. this cohort is also limited not only by the actual number of treated patients available to consult, but also taking into account we have only contacted English speaking families to avoid any question over interpretation and no families with less than 2 years post-treatment follow-up to ensure they have established treatment effect. The aforementioned international clinicians and patient organisations acknowledge that the UK clinical experience of MLD as a devastating and resource intensive condition is universal: ***"Early onset MLD results in the loss of the ability to walk, sit and talk within months of onset. The experience of children in the UK, with rapid loss of neurological function, is universally true for this disease".*** ***"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".*** ***"MLD universally results in profound neurological disability".*** According to data collected by one child's physicians, since diagnosis one child had: ***"1712 documented encounters with providers, 194 blood tests, 42 x-rays, 22 emergency room visits, 16 admissions (including 2 to PICU where she was intubated); has received 24-hour hospice care for 8 years, receives 12 medications each day for severe nerve pain, spasms, muscle tone, GERD, gut motility, stomach cramps, constipation, plus daily enemas. The child's bedroom is equipped with oxygen, a CPAP device, nebulizer, monitors for breathing, oxygen levels, heart rate, suction machine, cough assist machine".*** Clinicians and patient organisations consulted also indicated overwhelming support for gene therapy treatment: ***"Children who should be paralyzed, feeding tube dependent, non-verbal and terminally ill are leading remarkably healthy lives. They can walk, talk, see, attend school, make friends, breathe on their own and feed themselves".*** ***"[redacted], one of the world's leading gene therapy researchers, has described the results from Libmeldy as "stunning".***

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	"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".*** "***During our careers as paediatric neurologists with a specific focus on children affected by leukodystrophies, we have seen amazing advances in MLD with the development of gene therapy as an effective disease modifying therapeutic option".*** ***"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 life-saving 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".*** ***"I do not use this word lightly. It is a medical miracle. It is one of the greatest medical breakthroughs of our generation".*** The experience of patients and parents in the global follow-up survey is also comparable to that reflected in the UK (as seen in extensive patient and caregiver survey conducted by ArchAngel MLD Trust, The MPS Society and MLD Support UK in 2020): The follow-up survey had 13 respondents from 7 countries. (7 of these parents also took part in a recorded interview, a link to highlights of this is featured at the end of survey document). **All patients represented had significant time post-transplant: Late Infantile patients had a mean of 5.5 years (up to 10 years) post-transplant; Early Juvenile patients had a mean of 7 years (up to 8 years) post-transplant.** Not only do these mean durations exceed the average life expectancy of untreated patients, but this is lengthy outcome evidence when considering both paediatric rare disease and recent gene therapy approvals. **The survey records that treated patients demonstrate stabilisation and remarkable lack of symptoms across multiple domains which are fundamental to both quality of life and independence:** <u>Mobility</u>

	100% of treated LI children had a GMFC score of 0-2 and in fact the **majority of treated LI children had no issues: 57% GMFC 0; 29% GMFC 1; 14% GMFC 2**. **86% report total independence;** the remaining 14% (GMFC 2) reported categorisation due to use of leg splits for sports. **83% of treated EJ children were at GMFC 0-2**; 50% could walk/50% were wheelchair dependent. A minority of 17% were at the worst score GMFC 4, however reported a good quality of life which bore no comparison to untreated children at GMFC 4. <u>Self-Care</u> **100% of treated LI children were independent;** **33% of treated EJ children were independent**. Of the remaining 67% of treated EJ children, support required included minor help with transfer from wheelchair to shower and help with motor control for effective washing. <u>Cognitive</u> **100% of LI children were learning at the expected level for their age;** **50% of EJ children were learning at the expected level for age** 50% of EJ children were learning at a level below that expected for their age, however still achieving. Not only is working at a level below that expected for age true for many members of the general population, 'achieving' is a crucial acknowledgement, since **learning and moving forwards would not be possible without disease stability**. Academic regression is widely reported as a first symptom in untreated EJ cases and follows a rapid trajectory. <u>Speech</u> **100% of treated LI children have no speech problems;** **50% of treated EJ patients have no problems;** only 8% of treated EJ patients report 'significant problems'.

	Expert witness clinicians have previously given evidence stating that symptoms of pain, GI/feeding complications, seizures and frequent respiratory infections are particularly challenging and time intensive to manage in untreated patients. **The survey results reiterate the striking contrast to untreated patient in terms of the burden of disease management on both clinicians themselves and healthcare budgets**: Pain **100% of treated LI patients have no pain;** **50% of treated EJ patients have no pain.** 50% of treated EJ patients report 'some pain', however it is important to note that they report pain due to secondary complications commonly experienced by wheelchair dependent children, particularly during periods of growth, e.g. tendon retraction and muscle shortening. Expert witnesses have testified that such problems are prevalent across all conditions involving neuro-disability. GI **100% of treated LI patients have NO issues with GI/feeding/nutrition;** **100% of treated EJ patients have NO issues with GI/feeding/nutrition.** Seizures **100% of treated LI patients have NO seizures;** **100% of treated EJ patients have NO seizures.** Frequent respiratory infections **100% of treated LI patients have NO respiratory infections;** **100% of treated EJ patients have NO respiratory infections.** Medications **100% of treated LI patients have NO medication;**

	83% of treated EJ patients have NO medication. Hospital appointments **77% of all treated patients had no hospital appointments** (other than routine GT follow-up). The remining 23% report hospital visits for physiotherapy and tendon surgery. **There were 0 emergency hospital admissions.** **100% of treated children were attending school and receiving an education.** Children themselves also reported healthy social lives and participation in a wide range of activities. They supplied poems, diary excerpts, aspirations and even comments on gene therapy to the survey, demonstrating emotional maturity and good mental health, none of which would be possible in untreated children: ***"This week was my last one as a year five. My class went on a residential and it was so much fun. We got to go on the high ropes and we played in the lake on paddle boards. We stayed up late and watched England beat Denmark in the semi-finals of the Euros"*** ***"It feels so good to know that I have friends that I have had since before MLD. I love playing video games with my brothers and my mom yells at me like she does my brothers because I am on my phone too much".*** ***"I like that I am getting better at maths. When I am older I want to have my own shop and café called Teas and Toys".*** ***"Treatment was not fun, but it lets me have friends. I have a phone now. I run and play and talk to my friends. I make blankets for a scholarship for our school, and I go horseback riding".***
2	**Are the summaries of the criteria considered by the committee and the clinical and economic considerations reasonable interpretations of the evidence?** We strongly feel that unreasonable emphasis has been place on uncertainty of outcomes. Firstly, we do not believe that the committee has placed enough value on the demonstrated outcomes due to the heavy reliance upon, and negative interpretation of, GMFC scores and ARSA enzyme levels. Standardised definitions are two-dimensional and incapable of

	depicting what meaningful and functional physical and mental capabilities these children actually have in everyday life. Furthermore, we do not believe that the committee has placed enough value on the longevity of these demonstrated outcomes. Data of up to 10 years is amongst the most lengthy for recent gene therapy approvals in other countries. We believe the time post-transplant for the patients surveyed is long enough timeframe to demonstrate that patients have not only exceeded the lifespan of their older affected siblings or the comparator natural history cohort, but also that they have thrived and are living a normal life with no medical problems connected to MLD. We would therefore like to draw the committee's attention to the following illustratory statements from parents: ***"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. [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".*** ***"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".*** ***"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".*** ***"My son is six and a half years post-transplant, 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 after-school activities, such as swimming and Cubs. He is a typical 10 year old child with the absolute best quality of life".*** ***"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".***

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	"So [child] had his gene therapy ever since he's thrived. And he's been completely stable, all our follow-up checks have been really positive and we have no reason to believe that he will get any worse. So we look forward to a full and happy life for him." ***"[Child's name] has been stable now for five years. And by that, I mean, there are no signs of the disease progressing in terms of both her physical abilities, or her cognition. In fact, we've seen marked improvement in some areas. Her sensory processing issues, which were extreme have improved dramatically the rate at which she is learning and moving forward at school continues to surprise everyone around her, as does the pace of her emotional maturity".*** ***"Without gene therapy my son definitely would not been where he is now! Neither mentally nor physically".*** ***"My son, he's 5 years of age, has just completed two years of preschool, he's about to start mainstream Primary School. His quality of life is the very same as all his peers. He has extremely mild neuropathy, which means he has to wear lower leg splints when I take him football training. We go swimming, sailing. He enjoys life as much as all his friends and his little cousins".*** ***"My son got the treatment at the age of 11. Now he is 18 and is doing great. He is going to school, he has friends, he is independent… He studies media production in school and likes to make films, edit photos and make commercial posters and other such things. Last year he won a competition with a stop motion film with Lego figures that he made in school. It was about alcohol and that you shouldn't drink and drive".*** ***"[Children's names] are in mainstream normal classrooms where neither their classmates or their teachers are aware that either of them were born with a diagnosis of metachromatic leukodystrophy and that they underwent gene therapy. Neither of them receives any special services. They don't attend any doctors appointments that are extra, they are not on any medications. They do not have any therapies. And so their teachers and their peers are unaware of their diagnosis and that, in reality, neither would even be sitting next to the kids that they are making lifelong friends with".*** We also believe that the committee has placed unfair emphasis on uncertainty and given insufficient consideration to the non-financial and indirect benefits of the therapy to patients and their families, who testify: ***"To see stability means that we are given the gift of time. Time we shouldn't have had".*** ***"Being able to watch our son play video games and watch our daughter ride her bike and play with her friends and do all the things that her peers can do".***

	"Stability, is just an absolute gift to us as a family, a lifeline, when we were at the very bottom of the barrel, having both boys diagnosed in the same week with a terminal condition. But with the caveat of having a possible treatment for [child's name] it has been a lifeline for us and a life-saving lifeline for him and for us as a family". ***"We're living a relatively boring / normal life and this is all thanks to gene therapy. Our life looks pretty much like the next person."*** ***"Gene therapy doesn't just save the children's life, it saves the whole family and it saves them from having to go through the pain and suffering, that my eldest daughter had to endure because nobody should have to go through that".*** ***"I've seen it in my own family, the two boys are like, you know, it's like black and white. The difference is night and day. It's a certain death with MLD or given the gene therapy, the effectiveness of it, it's a full and happy life".*** ***"This treatment has quite simply enabled us to have a normal life with the exception of needing to consider accessibility issues wherever we go, like millions of other wheelchair users. So we go to the swimming pool. We go to restaurants, we go to the theatre, we go to art galleries, we've been to some spectacular huge events like Royal Ascot and we've enjoyed many holidays". in far-flung locations. My husband is also able to run a successful business full time and I'm able to run a charity helping other families".*** ***"We still don't know much about gene therapy, but what we do know is we are busy living and not busy dying and we know that, you know, dying is the one thing that is certain with an MLD diagnosis".*** ***"Thanks to Gene Therapy I get to be 100% mum. Not 20% nurse 20% admin 20% voice for my child to get what they need 10% dietician 10% physio 10% OT 5% counsellor to the rest of the family and what little is left as mum.."*** **No mental health issues were attributed to the carer burden of treated children.** This is in stark contrast to the experience of parents of untreated children, who report significant mental health issues including **intense grief, extreme stress, depression, anxiety, panic, isolation, anger, guilt** as they care for their declining child. Families who have both treated and untreated children have articulated some of the extreme contrasts as follows:

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	"When my eldest daughter graduates from college next June, I have no idea how I will attend her commencement ceremony because her college is 400 miles from our home. By my calculations, I have not left the state of Pennsylvania more than six times since 2012. I am almost never more than 30 minutes from my home in case we need to go to the hospital…I have spent three of the last six Christmas in hospital". ***"It is impossible to calculate the trauma [my child's] older brother and sister have experienced because of MLD. Both have suffered from depression and anxiety".*** ***"There is a painful longing, an absence within my family, among my other children, with the loss of a child. The value is seeing [children's names] living a life that their sister was never able. Milestones, excitement, joy, a good grade, attending sporting events, playing sport, shooting baskets in the back. These are all things that their sister was never able to do. And the value can never be underestimated, it's priceless".*** ***"My elder daughter experiences panic attacks and anxiety, constantly fearing the worst in all situations, all due to the trauma of seeing the devastation caused by MLD".*** ***"We're able to live as a normal family, we go out to work, the boys go to mainstream school. I've been able to open my own coffee shop…it also enables us to look forward, which with an MLD diagnosis we don't normally want to do that, the last thing we want to do is think about the future. But thanks to their disease stability, we're able to look forward to the future with the boys".*** We also do not believe that the impact of the death of an untreated patient has been fully taken onto account. Death does not remove the problem and stop all MLD related expenses. As one global MLD patient organisation points out: ***"Although the patient's direct expenses may cease, the impact on the family is a longstanding one as they grieve and process the loss of their child. Many parents divorce or create single parent families that need governmental support, depression is common as is loss of personal and professional work productivity which often leads to job loss. Emotional toll includes not only parent but non-MLD siblings and extended family".*** We believe this needs to be given greater consideration when establishing the value of the therapy and when comparing the value to the direct and indirect costs of no therapy.

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3	**Are the provisional recommendations sound and a suitable basis for guidance on the use of OTL-200 in the context of national commissioning by NHS England?** We do not believe that the provisional recommendations are a sound and suitable basis for the guidance on the of use of OTL-200 by NHS England for the following reasons: Additional evidence supplied in order to address uncertainties needs to be taken into account. The fact that the patients, families, patient organisations, clinicians and pharmaceutical company emphatically do not share the same opinion as NICE on uncertainties needs to be given greater regard. An equitable balance of uncertainty with the certainty of non-treated patient outcomes and lifelong impact on families is not demonstrated. We believe that the evidence has already demonstrated that the list price is less than a lifetime of medical care for typical untreated patient. We are not convinced that impacts not just through to end of patient lives, but over the lifetime of the immediate family, have been fully considered. These impacts include the emotional and psychological well-being of carers, the ability to access education and social interaction of affected children who have a chance to grow up and lead 'normal' lives, work productivity gains for parents/caregivers, family finances and outside sources of financial support. The strict mathematical calculations which are applied in the assessment of all technologies do not seem equipped to factor in the nuances of such a rare and severe condition as MLD. We do not believe the provisional recommendation reflects a full consideration of all potential solutions to balance any uncertainties with a risk sharing approach. The pharmaceutical company have publicly indicated willingness to adopt a creative payment model and we believe this price 'negotiation' should be of the utmost priority before any final decision is taken. We believe that the committee should consider how data could be continued to be gathered and reviewed in order to allow a 'conditional' recommendation. This would allow patients the opportunity to benefit from treatment before it is too late. Considering the very small number of patients potentially eligible for treatment – less than 5 per year - this would not add any significant financial risk to NHSE. Given the demonstrated safety and efficiency of treatment nor would it imply any clinical or therapeutic risk to patients.

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	The provisional recommendations do not acknowledge the significance of this ground-breaking treatment either as a step-change for MLD or as an important milestone in the rapidly changing landscape of science and technology. As one of the global MLD organisations commented: ***"NICE should be rejoicing in the achievements of British pharma to make miracles possible for patients impacted by MLD and similarly devastating monogenic disorders. Libmeldy will usher in a new era for genomic medicine…This is a moment for the NHS to celebrate the visionary leadership of the UK's biotech sector."***
4	**Are there any aspects of the recommendation that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?** We do not believe that there is any discrimination to the groups mentioned above. However, we feel compelled to point out that the current recommendation does discriminate against patients diagnosed with MLD and their families in the following ways: By focussing upon therapeutic uncertainties, assuming negative future outcomes and not taking into account the potential for positive future outcomes. Not only are treated children currently remarkably different to untreated children, there is absolutely no evidence to indicate that treated children do not have the potential to be fully contributing members of society in the future. In fact, parents have reported a number of successes and distinctions which their treated children have achieved when in competition with healthy peers which is arguably evidence to suggest that these children have potential to be high achievers in many aspects of life. By upholding 'completely normal' as the desired outcome. We do not believe this benchmark is consistent with other technology appraisals. For the treated patients who have demonstrated what is deemed to be a 'partially successful' outcome, this recommendation undermines the value of their lives and their contributions to society. As one patient organisations states: ***"MLD gene therapy patients can and are living extraordinary lives even when their peripheral nerves are not commanding their bodies to be the fastest, most nimble or refined in their movements".***

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	There is discrimination to MLD patients by taking a negative view of the inherent small patient cohort. Issues such as the rarity of the disease, size of the natural history cohort and lack of confidence in affected sibling data as comparator is unfair. Evidence parameters which exist within assessment frameworks are not always achievable in rare diseases, as one patient organisation concurs: ***"MLD is rare and no single country will have the patient numbers typically that typically inform on financial health decisions. This limitation, however, should not obscure the unparalleled opportunity gene therapy provides to change the course of these children's lives"*** Any insistence on waiting for additional data, despite the excellent data we already have including over 10 years post-treatment follow-up, feels unreasonable. We believe the current recommendation unfairly discriminates against newly diagnosed families with MLD by undervaluing this therapy, which may lead to limited or no access to treatment for UK patients. The amount of data required by NICE would only be possible if newborn screening were already in place. One of the fundamental impetuses for establishment of ArchAngel MLD Trust was to help more patients to access this transformational therapy, based on personal experience of treatment and close relationships with other treated families. Since the majority of treated patients were identified due to an elder untreated sibling – and the majority of untreated patients diagnosed too late to be eligible for treatment - one of main focuses of our work is newborn screening, in order to guarantee diagnosis for timely intervention. According to WHO criteria, newborn programmes across the globe require viable therapies such as this in order to qualify for consideration of addition to a newborn bloodspot test. The current recommendation would discriminate against future UK MLD patients by thwarting the possibility of their diagnosis via newborn screening. We also believe that the current concerns about the scope of the cryopreserved process are unreasonable and discriminatory. Blood products are very often frozen for transport, ex-vivo gene therapy uses a normal blood product. There is no evidence that freezing blood products would impact the genetic modification. Preventing patients access to therapy on the basis of the cryopreservation aspect is not justified and therefore discriminatory.

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	[**MLD Support Association UK**]
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	[**None**]
Name of commentator person completing form:	[redacted]

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	Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	We are concerned that a figure of 15 years has been taken as the length of stability following OTL-200. There is much evidence in the UK and also in the global community that, after successful engraftment, HSCT has provided stability for MLD for 30+ years. As OTL-200, also post successful engraftment, provides gene-corrected haematopoietic stem and progenitor cells it is difficult to see why this stability and production of cells should not also go beyond 30 years as HSCT has done in later-onset MLD. If a stable period of 30+ years was accepted then this would dramatically alter the cost-effectiveness of OTL-200.
2	The Committee concluded that "the evidence for each of the EJ subgroups was extremely uncertain because of the low patient numbers". Therefore, MLD Support Association, ArchAngel Trust and the MPS Society has carried out a Global survey of treated patients (See Survey 2021 – Metachromatic Leukodystrophy Review of gene therapy treated patient outcomes, shared with NICE).. There were 13 families across 7 countries – 7 LI (late-Infantile), 1 PS EJ (pre-symptomatic Early Juvenile) and 5 ES EJ (Early symptomatic Early Juvenile). • The data was shown to be comparable to the UK patient, parent/carer burden survey. • Data shows stabilisation across multiple domains • 100% of LI patients reported to have a good quality of lie and disease stability across all medical domains • 83% of EJ patients reported to have a good quality of life and disease stability • Children and young people have a god quality of life, have aspirations, strong peer support, friendship and active social lives that are not restricted in any way. • 100% of LI's were in full time mainstream education. • 83% of EJ were in full time education with 50% attending a mainstream school • The parent carer burden was much reduced compared to the burden of caring for an untreated child. However, the most amazing evidence was given by the children/young adults themselves: "It means a lot to me because I can make friends and do things with other people. I hope one day the disease will not take kids like my sister." "Treatment was not fun, but it lets me have friends and I have a phone now. I run and play and talk to my friends. I can run better than xxx … I am happy to be here with my family. Thank you for treatment". "I can play with my sister". The quotes from the parents also give an insight into the normality of life, yet tinged with great sadness of older untreated siblings: "Seeing a vibrant life lived in memory of her sister who wasn't able to be treated." "A normal life for our child and that he is not condemned like his brother." "Our perspective is not unique but I really feel that it is impossible for those who have not witness it to appreciate the difference this therapy makes and the consequences of not administering it when needed." "Our daughter is almost 9 years post diagnosis and she is an inspiration to many….She is in school

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	thriving. She would not be riding, swimming, playing, showering on her own, dressing on her own, singing in chorus and so on without Gene Therapy (GT). How can anyone look at her and not think that GT is worth it…" "We still don't know much about gene therapy, but what we do know is we are busy living and not busy dying and we know that, you know, dying is the one thing that is certain with an MLD diagnosis". ""I do not use this word lightly. It is a medical miracle. It is one of the greatest medical breakthroughs of our generation and I am so honoured to be part of, to have witnessed, to have had a front-row seat to the biggest medical breakthrough in a generation". On disease stability of medical symptoms the survey shows: GI/Feeding/Nutrition – LI and EJ 100% no symptoms Behaviour – LI 100% no symptoms and EJ 83% Seizures – LI and EJ 100% no symptoms Hearing – LI and EJ 100% no symptoms Scoliosis – LI and EJ 100% no symptoms Frequent respiratory infections – LI and EJ no symptoms Medication required – LI 100% no symptoms and EJ 83% no symptoms Hip dislocation – LI 100% no symptoms and EJ 83% no symptoms The survey shows children leading a normal life, attending mainstream schools, playing with their friends and enjoying activities like football, horse riding, swimming, dancing. They do not have frequent visits to emergency medical services. They do not have prolonged stays in paediatric intensive care units (PICU). At the end of this survey is a link to video testimonies of the survey participants. Please watch this to gain a full understanding of MLD and the life-saving benefits of Gene Therapy. We believe that the outcome of this survey shows not only the clinical cost-effectiveness of OTL-200, but also the amazing gift to families who are able to lead normal lives..
3	The ECD suggests that there is a problem in identifying patients with ES-EJ who would be eligible for treatment. However, the company has stated that eligibility criteria have been modified over the years of the clinical trials. Also, clinical experts have confirmed that discussions and decisions concerning individual patients would be carried out at a multi-disciplinary level prior to recommendation for treatment.
4	We do not believe that the provisional recommendations are a sound and suitable basis for guidance on the use of OTL-200 in the context of national commissioning by NHS England because it does not give enough weight to the suffering of affected children and their families. MLD Support Association UK has been supporting families affected by MLD for almost 10 years. We see treated and untreated children regularly. The comparison is black/white or night/day. Week in week out we see the suffering of the untreated children, their parents and their siblings. We have an active Facebook group and the families keep in touch so we get to hear about midnight rush to hospital, frequent infections, gastro-intestinal problems, seizures etc. We hear of the weeks spent in PICU (paediatric intensive care unit), weeks spend in HDU (high dependency unit). We hear about the pain suffered by children who cannot move, speak, see or hear. We hear about the multiple medications required to try and keep the children comfortable. We hear about the misery, grief, guilt and agony of having to discuss "end of life" arrangements for a young son or daughter. We see families who are trapped at home because it is too difficult to go on holiday or take days out. We see unaffected or treated siblings forced to lead a restricted life because of their affected sibling.

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	But, most of all, because of OTL-200, we see families returning to normal after the untreated child dies and the treated sibling carries on a normal child's life. This is the black and white, night and day. The untreated child affects the entire extended family, whereas the treated child is just "normal". MLD Support Association does not believe there is any good reason to deny life to a child when it is available and we know it works. As treatment is available to children in the USA and in Europe, we do not see why it should not be available to children in England.
5	
6	

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	[redacted] The MPS Society MPS House Repton Place, White Lion Road Amersham, Bucks HP7 9LP
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
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Example 1	We are concerned that this recommendation may imply that ……..
1	We are worried that the committee concerns over the longevity of treatment effect may overshadow the transformational outcomes of this treatment. Whilst we appreciate their acknowledgment that this treatment is innovative and a step change in the treatment of MLD, long term uncertainty still appears to be a key decision making criteria. Whilst we acknowledge long term stability is always a key criteria for NICE, this is always going to be uncertain, in ultra-rare disease populations like MLD and it is important that NICE review the value and richness of the data and testimonials from patients, parent carers and clinical experts to prevent causing health inequalities in this patient cohort. Allogeneic HSCT for MPS disorders has been used for over 30 years. Clinical experts have confirmed that if successfully engrafted, functional enzymes are released for the patient's lifetime. Given that OTL-200 uses the same approach for its gene therapy, it is my understanding that sustainability of enzymes would also happen in MLD treated patients. Whilst longevity is unknown, we have tried our best to evidence long term stability and the transformational outcomes of this therapy for patients and carers through two surveys ***(MLD patient and carer burden survey, December 2020; MLD review of gene therapy treated patient outcomes, August 2021 – submitted to NICE for review),*** clinical testimonies and reports and a patient video**(all submitted to NICE).** Parent and carers have specifically reported; *"My son is six and a half years post-transplant, he was treated in December 2014, he is in full time mainstream education and he doesn't require any additional support"* *"Gene therapy doesn't just save the children's life, it saves the whole family and it saves them from having to go through the pain and suffering, that my eldest daughter had to endure because nobody should have to go through that".* *"I do not use this word lightly. It is a medical miracle. It is one of the greatest medical breakthroughs of our generation and I am so honoured to be part of, to have witnessed, to have had a front-row seat to the biggest medical breakthrough in a generation".* *"Thanks to Gene Therapy I get to be 100% mum. Not 20% nurse 20% admin 20% voice for my child to get what they need 10% dietician 10% physio 10% OT 5% counsellor to the rest of the family and what little is left as mum.."* *"Treatment saved not only my child's life…. But that of my own and their dads"* *"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,*

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	singing in chorus and so on without Gene Therapy (GT). How can anyone look at her and not think that GT is worth it. SHE is alive and she is THRIVING because of GT".
2	In regards to the concerns over the decline in ARSA CSF, we feel it was important to emphasise that the clinical experts were not concerned by these declines. Their interpretation was that the results would still be within the normal range and therefore from a clinical view they would be classed as responders. They also emphasised the importance of not focusing solely on the data when making decisions but to also look at both the clinical evidence and patient reported outcomes. In rare diseases, we often see that a patient's lab and clinical reports do not always correlate with how the patient presents or feels. It is critical to assess and review outcomes based on disease understanding rather than what is normal compared to the general population.
3	Despite the reports and the discussions around MLD being a worse health state than CLN2, the committee's decision not to recommend treatment for the eligible population is incredulous. Particularly given that CLN2 has reimbursed treatment through a Managed Access Agreement (MAA). Would a MAA or National MDT committee not be something NICE would consider, particularly in answering some of those uncertainties within the Early Juvenile Population?
4	In order to further evidence disease stability within this small patient cohort, patient organisations have collected further data from 13 treated patients (7 late infantile (LI) and 6 early juvenile (EJ)) globally ***(MLD review of gene therapy treated patient outcomes, August 2021 – submitted to NICE for review).*** We focussed on the areas of uncertainty raised in the ECD, concentrating on health related Q of L parameters. Across all area 100% of LI and 83% of EJ reported long term stability. **Mobility** -86% of LI were full independent with walking with only 13% reporting the need for leg splints when doing sports. Whilst 50% of EJ patients were fully wheelchair dependent **Self care** - 100% LI were independent 33% EJ were independent. The remaining 67% required some support **Cognitive function** – 100% LI and 50% EJ of patients were working towards expected levels for age. The remaining 50% EJ, whilst not at expected levels were still achieving. All LI were in full time school. 83% were in full time school. **Pain** – 100% LI and 50% EJ reported no pain. Pain reported was due to secondary complication common during wheelchair dependency and growth. **Wider medical symptoms** – All LI reported no symptoms across 11 commonly associated symptoms of MLD. Whilst there were some symptoms seen in the EJ population in most instances the severity was nowhere near that seen in the untreated population. This was reflected in no patients requiring emergency hospital care or admissions. In the MLD patient carer burden report ***(December 2020)*** submitted to NICE we reported an average of 18 visits for LI and 14 visits for EJ untreated patients. **Parent carer burden** – 100% of respondents agree that the Q of L of parent / carers and individuals was 100% better than non-treated. **Reports from parent's and carers** *"To see stability means that we are given the gift of time. Time we shouldn't have had. To think of the boys having to go through what their sister did is just in comprehendible. And this disease stability is a miracle and will be forever grateful"* *"Stability, is just an absolute gift to us as a family, a lifeline, when we were at the very bottom of the barrel, having both boys diagnosed in the same week with a terminal condition.* *"xxxxx and xxxxx, are in mainstream normal classrooms where neither their classmates or*

	their teachers are aware that either of them were born with a diagnosis of metachromatic leukodystrophy and that they underwent gene therapy. Neither of them receive any special services. They don't attend any doctor's appointments that are extra, they are not on any medications. They do not have any therapies. *"We're living a relatively boring / normal life and this is all thanks to gene therapy. Our life looks pretty much like the next person."* **Reports from children treated with gene therapy** *"It feels so good to know that I have friends that I have had since before MLD. I love playing video games with my brothers and my mom yells at me like she does my brothers because I am on my phone too much. I know movies and can remember so many lines that make me laugh and then I repeat them and make my family laugh. I love my family"* *"I am always happy, I always try my best, I like that I am getting better at maths. When I am older I want to have my own shop and café called Teas and Toys"* *"Treatment was not fun, but it lets me have friends and I have a phone now. I run and play and talk to my friends. I make blankets for a scholarship for our school, and I go horseback riding. I can run better than xxx and it is because I was treated younger. I am happy to be here with my family. Thank you for treatment"* *"It means a lot to me because I can make friends and do things with other people. I hope one day the disease will not take kids like it did my sister"* *"I can play with my sister"*
5	Whilst we recognise NICE's acknowledgement over the credibility of the patient and clinical testimonies, we were still concerned over the level of uncertainty raised, over whether the data represented the wider treated population and clinical opinion. Whilst NICE only allows a small representation of clinical and patient experts at the committee, the patient groups as part of their submission presented the clinical opinion of a further 5 UK experts. In total, all three of our paediatric UK specialist centres were given the opportunity to share their opinions and views as well as two adult centres. To further evidence the global view on gene therapy for MLD we have submitted to NICE an additional survey focusing on the treated LI and EJ population (***MLD review of gene therapy treated patient outcomes, August 2021)*** and letters of support from international clinical experts and patient organisations. In summary they have said the following: A leading professor in paediatrics and lysosomal disorders in the USA, states –*"truly remarkable and well outside anything than can be achieved with standard transplant. This dramatically effective therapy that will be life changing and life saving for patients with MLD"* A chief of Neurology in the USA, states *"Gene therapy is the best option to halt this devastating disease, as HSCT offers only mixed outcomes. With gene therapy, children have the chance to have normal lives"* Further specialist team in the USA state, *"in our clinical and research experience, there is strong support for gene therapy as the best therapeutic option"*
6	In response to the committees concerns over the borderline eligibility and cost to the NHS for patients

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	who become ineligible during harvest and transplant. I am not sure what the concerns are in relation to cost. It is my understanding that if untreated, the cost to the NHS would be the same as the untreated population.
7	We do not agree that the provisional recommendations are a suitable basis for guidance to the NHS and hope that the additional clinical and patient reported evidence provided to NICE will better inform the committee's conclusion to recommend this transformational therapy for both the eligible LI and EJ MLD population.

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Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	[**I participated in advisory boards organised by Orchard Therapeutics**]
Name of commentator person completing form:	[**Paul Gissen**]

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Example 1	We are concerned that this recommendation may imply that ……..
1	I disagree with the committee's decision. It is a dangerous delay of approval for the drug that has shown good efficacy in specific groups of patients with MLD. This means that the UK patients will suffer from a progressive neurodegeneration that could have been arrested.
2	The committee has not given sufficient consideration to the stabilisation of the brain MRI appearance as evidence of disease stabilisation in patients treated with OTL-200.
3	Whilst it is difficult to model the number of years of stabilisation without real-life data it is likely that the average number of years that the patients will stabilise for would be higher than estimated by the ERG, who are very conservative in their calculations. The effect of HSCT in other lysosomal storage disorders has been studied for longer than 40 years and it is a good model for predicting disease stability after treatment with OTL-200.
4	I believe that with appropriate patient selection the majority of treated patients will have excellent response and the committee's suggestion of <50% full response is an underestimate.
5	
6	

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
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- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the appraisal consultation document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

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OTL-200 for treating metachromatic leukodystrophy [ID1666]

Consultation on the evaluation consultation document – deadline for comments 5pm on Friday 30 July 2021 - email: NICE DOCS

NICE, its officers or advisory committees.

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NICE National Institute for Health and Care Excellence

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	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Evaluation Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	[Dr James Davison, Great Ormond Street Hospital]
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	[Dr Davison has participated in Advisory Board for Orchard Therapeutics and had informal discussion with Orchard Therapeutics about healthcare cost modelling for the technology. He was investigator on observational study of MLD (IRAS 279868), study sponsor Orchard Therapeutics.]
Name of commentator person completing form:	[**Dr James Davison**]

Comment number	**Comments** Insert each comment in a new row.

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Example 1	We are concerned that this recommendation may imply that ……..
1	All relevant evidence appears to have been taken in to account.
2	**I have only had access to the heavily redacted Committee Papers which limits my comments on interpretation of the conclusions drawn**. In terms of the long-term stability of the technology, long-term engraftment would be expected, and no specific reason to consider that there would be loss of the integrated gene product within the engrafted cells. The cerebrospinal fluid (CSF) enzyme levels referenced do not correlate directly to clinical outcome. Extrapolation from the observed CSF enzyme levels to predict future trends is problematic, and I would disagree that one should assume further decline as the ERG proposed. In patients with other lysosomal disorders including mucopolysaccharidosis (MPS) I and MPS II who have received standard HSCT, and who have consistent high level donor cell engraftment, enzyme levels in plasma/ white cell assays do stabilise but can fluctuate over time.
3	The numbers of patients included in each sub-category are small, and it is also problematic to extrapolate from sub-analysis of these groups with wide confidence intervals in terms of the long term outcome. From a clinician's perspective, there is a very significant qualitative improvement in the outcome for patients who have been treated with the technology compared to those not treated, as substantiated in the comments in section 4.26
4	
5	
6	

Insert extra rows as needed

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	
Name of commentator person completing form:	Nicola Elson

Comment number	**Comments** Insert each comment in a new row.

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	Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	I am concerned that the committee did not fully comprehend how treated children in GMFC 3 or 4 and untreated children with the same GMFC score are in very different places medically. MLD is a multisystemic condition and as such it is wholly inappropriate to compare one or two elements. Treated children with a score of 3 of 4 do not suffer with seizures, they are not peg fed with huge gastro problems, they don't have dystonia, scoliosis or dislocations, they are not in constant pain requiring a cocktail medication to keep them comfortable and cognitively they are in a far better place. This is quite clearly demonstrated in the Metachromatic Leukodystrophy Review of Treated Patients Survey 2021 (shared with NICE). The feedback from families indicates these children have minimal medical symptoms, the majority are in full time education and participating in additional activities/clubs and 100% of respondents reported no requirement for any emergency hospital admissions in the last 12 months. Having met a good number of treated and untreated children, the most instantly striking difference is that treated children engage and interact with you with no effort or encouragement. They are listening, looking and responding to you, they are laughing and giggling, they are happy children and generally enjoying life. It's impossible to compare treated and untreated children and therefore, in my opinion, wrong to do so.
2	With regard to caregiver/parent burden and having spent time with many families of treated and untreated children, I feel it is important to point out there is far greater burden on those caring for an untreated child. This is primarily due to the fact these children are far more poorly and need significantly greater medical intervention and support. There are wide ranging consequences which result from caring for a medically vulnerable child and it is my opinion that the less care and medical interventions a child requires the less strain, guilt, grief, phycological and emotional turmoil the families/caregivers suffer. The more able and clinically well the child is, the more independent they are and able to engage and interact with others. This reduces the burden on the family substantially, with both the treated child and other family members having a fairly typical life. The child can attend school with minimal disruption due to illness, take part in extracurricular and social activities. The parents can continue to work, siblings are able to have a social life, there is no constant reliance on the goodwill of neighbours, friends and family to provide help and support. Holidays, days out and family parties do not become a thing of the past. One respondent of the Metachromatic Leukodystrophy Review of Treated Patients Survey 2021 state's 'Thanks to Gene Therapy I get to be a 100% mum. Not 20% nurse, 20% admin. 20% voice for my child to get what they need, 10% dietician, 10% physio, 10% OT, 5% counsellor

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	to the rest of my family and what little is left as mum' Other responses of the survey show resolutely the feelings of the families regarding their hope and aspirations for their child and they speak volumes. 'A normal life' 'graduate' 'married' 'thriving' and 'hope for the future' are just some of the words and phrases these families are able to use as a direct result of this treatment.
3	This evaluation implies there is practicality issues and difficulty in identifying patients who are ES-EJ for whom treatment would be beneficial. The company has stated the eligibility criteria has been modified appropriately over the last ten years. The clinical experts have also addressed this matter by confirming discussions and decisions concerning individual patients would be carried out at a multi-disciplinary level.
4	I would request that the Committee reviews the attached links to a Children in Need video and Orchard Therapeutics video, in order to fully understand the verbal discussions on the night and day comparison of treated versus untreated children. https://www.youtube.com/watch?v=85OZDPRNoVI&t=6s The Elson Family – Orchard Therapeutics (orchard-tx.com)
5	My Son has asked me to forward the following letter:

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	Dear NICE It was the last week of the School year this week. My class got to go on a residential, I went too. We got to go on the high ropes and play in the lake on paddle boards. We stayed up late, Watched a movie and had a midnight snack. James and Noah are my best friends, we have been friends forever, we started nursery together and we will start the next School year together. Every thing I can do like Swining, bike riding, playing computer games, and playing with my friends is all because of Gene Therapy. I wouldn't be able to do any of the things I love without this treatment and the Doctors and nurses in Italy are Hero's. If my Sister had the treatment, She could have done the things She loved and I don't want other people to not be able to do the things they love. I am upset and angry that other people wouldn't want other people to have this treatment too. From J
6	

Insert extra rows as needed

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Comments on the ECD received from the public through the NICE Website

Name	[redacted]
Role	Public
Other role	
Organisation	
Location	
Conflict	
Notes	
Comments on the ECD:	
If this treatment has the potential to stop MLD progressing and can give quality of life to the children affected (and families affected too), then I fully support that this should be approved for a trial at the very least. I cannot understand why it wouldn't be perused when it has the potential to make such a difference to these children's lives. I have witnessed the destruction that MLD causes through my friends child who has this disease. It's not only the child, but the whole family who suffers. Please please approve the use of this treatment.	

Name	[redacted]
Role	Patient/ carer
Other role	
Organisation	
Location	
Conflict	
Notes	
Comments on the ECD:	
How is this acceptable. How can you look a family in the face and tell them that the UK have declined treatment for MLD. That your child's quality of life is not worth treating. That your time as a family is not worth every moment. It's hard enough hearing your child has a degenerative disease but to know that if we had caught it sooner of if there was treatment available over here that we could have prolonged even saved Milos life-that is the toughest part to accept. As parents we felt helpless	

Name	[redacted]
Role	Public
Other role	
Organisation	
Location	
Conflict	
Notes	
Comments on the ECD:	
The children with this condition really need to be given the opportunity to have this treatment. If there is an opportunity to slow or even halt the progression of the disease it needs to be taken. The impact on the whole family where a child is diagnosed with this condition is massive, parents have to leave work to care for the child putting a greater strain on family finances, they need specialised equipment and the house needs to be modified. The siblings can often find they are struggling to have their full needs met. Parents are exhausted and having a child who needs immediate care for what ever reason can supersede the the	

child who does not have this condition. These siblings can become young careers too due to the exhaustion and deep dark place the parents finds themself in . Equipment to support the children with this diagnosis can often need to be raised for by a fund raising appeal - nothing given to the parents to get out of the house like a suitable car- these parents do not want to have to receive support through charity . The pressures on the parents relationships can be huge . Finally , these children deserve the opportunity to have this treatment if it can halt the disease or improve their quality of life there cannot be any reason not too.

Name	[redacted]
Role	Public
Other role	
Organisation	
Location	
Conflict	
Notes	
Comments on the ECD:	
Not making this treatment available to children who suffer from late infantile and early juvenile MLD is not taking into account that these lives Matter too. Treatment for this horrible disease needs to be made available for children in these age groups.	

Name	[redacted]
Role	Public
Other role	
Organisation	
Location	
Conflict	
Notes	
Comments on the ECD:	
I am completely at a loss as to why you have come to the decision to no longer recommend the treatment OTL-200. As a consequence of this decision you will be denying you g children and babies to have at least a fighting chance at life. I sincerely hope this decision is overturned.	

Name	[redacted]
Role	Public
Other role	
Organisation	
Location	
Conflict	
Notes	
Comments on the ECD:	
I know a local family who have 2 children with MLD. Unfortunately the eldest child was already showing symptoms and could not be saved, but the younger child has been saved by this treatment and is a happy healthy young boy. It's awful enough having to watch one child go through this disease, but thinking it might gave been both children had this treatment not been available is unbearable. This treatment is proven to save lives. By making this treatment unavailable you are denying life to	

so many children. Why would anyone want to do that? These children are not just statistics they are someone's whole world and are loved and cherished.

Name	[redacted]
Role	Public
Other role	
Organisation	
Location	
Conflict	
Notes	
Comments on the ACD:	
Please reconsider your decision, this treatment saved a child from developing this disease. It works.	

Name	[redacted]
Role	Public
Other role	
Organisation	
Location	
Conflict	
Notes	
Comments on the ECD:	
I have known people with MLD who have received treatment and they are healthy and active. Those who have not had treatment live a life of pain and suffering.	

Name	[redacted]
Role	NHS professional
Other role	
Organisation	
Location	
Conflict	
Notes	
Comments on the ACD:	
I am a paediatric BMT consultant, and the Programme that I lead is the largest metabolic transplant centre in Europe. Manchester has transplanted many hundreds of children with lysosomal storage disease, and other metabolic diseases. Much of the information about long term outcomes in stem cell transplant are extrapolated from transplant in similar disease, including Hurler Syndrome. Donor derived leucocytes provide enzyme to cross correct residual enzyme deficient tissue after allogeneic transplant. Engrafted stem cells provide enzyme competent leucocytes over the remaining lifetime of the patient. I was surprised by the NICE rejection of the MLD case. My comments are those of an expert in metabolic disease stem cell transplant, and I have no conflict of interest to declare. I would like to make certain points about HSC transplant therapy of metabolic diseases, and that this treatment attenuates disease, including in the long term, offering significant improvement to quality and length of life. This is very likely to be the case for MLD HSC GT, and not to treat appropriately selected children with this condition would indeed be a missed opportunity. Transplant is never curative, and	

the outcomes of transplant are supported by organ-specific interventions within he context of a well-functioning and disease focused MDT.
When I read the data for GT in MLD, then the results are so much better than the results of our commissioned and funded allogeneic interventions in BMT.

- There is sustained engraftment of gene-modified HSC in the MLD HSC-GT therapy. We know from allo-transpant experience that this is likely to be both maintained for the long term and associated with a continuing disease response.
- We know little about the relationship between CNS enzyme or substrate and disease response, even in a responding neurological disease, such as Hurler. We also know little about the natural history of enzyme levels and substrate levels i the CSF, and they should not be used to inform clinical outcomes.
- There may be difference in different long-term outcomes. Within a responding patient then different organs may respond differently
  - We transplant children with Hurler syndrome and the skeletal outcomes are poorer than the CNS and somatic (cardiac etc) outcomes
  - In MLD following allo-transplant then the response in the CNS (cognitive outcomes) are better than motor outcomes (neuropathy) outcomes, suggesting that the CNS is easier to correct
  - In Hurler very good quality of life is maintained even when motor scores are poor, as skeletal disease is relatively poorly corrected. This does not mean that transplant has not been effective in modifying disease and giving good quality of life. Something similar may occur in children- especially those transplanted with more disease manifestations – in MLD
- Disease response following transplant in metabolic diseases is complicated and is principally affected by 3 factors
  - Genotype and children with milder disease will necessarily do better than children with severer disease, whatever treatment is offered
  - Age at transplant – engraftment and enzyme delivery to different compartments is not immediate and the underlying disease will progress as this enzyme is delivered, and os the older children and those with disease manifestations will fare less well in the long term since HCT is better at preventing disease progression than it is at reversing established disease
  - The enzyme delivered by the engrafted leukocytes and this is clearly optimised by the supraphysiological enzyme of the gene modified transplant